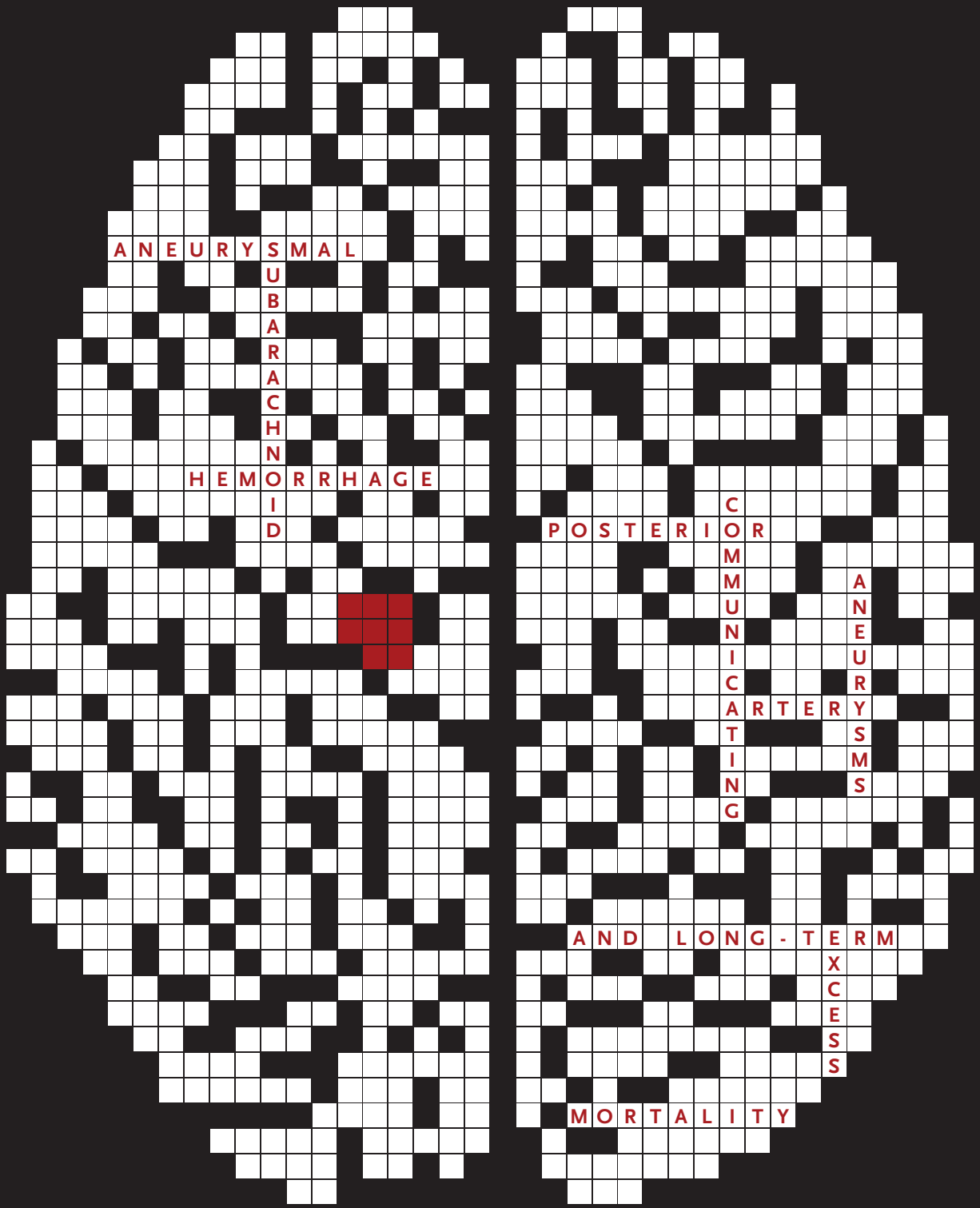

Justiina Huhtakangas
Helsinki 2018

Aneurysmal Subarachnoid Hemorrhage
Posterior Communicating Artery Aneurysms and Long-Term Excess Mortality

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Academic Dissertation

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Original publications

This thesis is based on the following publications:

I Huhtakangas, Lehecka, Lehto, Jahromi, Niemelä, Kivisaari: *CTA Analysis and Assessment of Morphological Risk Factors related to Rupture in 413 Posterior Communicating Artery Aneurysms.* Acta Neurochirurgica. 2017;159:1643–1652.

II Huhtakangas, Lehecka, Lehto, Jahromi, Niemelä, Kivisaari: *Occlusive Treatment of Ruptured Posterior Communicating Artery Aneurysms Riskier than Expected Treatment and Outcome of 620 Consecutive Patients.* Accepted for publication in Journal of Neurosurgery 4/2018.

III Huhtakangas, Lehto, Seppä, Kivisaari, Niemelä, Hernesniemi, Lehecka: *Long-Term Excess Mortality after Aneurysmal Subarachnoid Hemorrhage – Patiens with Multiple Aneurysms at Risk.* Stroke. 2015;46:1813–1818.

Abbreviations

AChA ..... Anterior Choroidal Artery
aSAH ..... Aneurysmal Subarachnoid Hemorrhage
BRAT..... Barrow Ruptured Aneurysm Trial
cRSR..... Cumulative Relative Survival Ratio
CE..... Contrast Enhaced
CI..... Confidence Interval
CT..... Computed Tomography
CTA ..... Computed Tomography Angiography
DCI ..... Delayed Cerebral Ischemia
DSA ..... Digital Subtraction Angiography
EKG ..... Electrocardiogram
EVD ..... Extra-ventricular drainage
GOS..... Glasgow Outcome Score
HH ..... Hunt & Hess (scale)
ICA..... Internal Carotid Artery
ICP..... Intracranial Pressure
IEL ..... Internal Elastic Lamina
ISAT..... International Subarachnoid Hemorrhage Trial
ISUIA..... International Study on Unruptured Intracranial Aneurysms
MRA ..... Magnetic Resonance Angiography
mRS ..... Modified Rankin Score
ONP ..... Oculomotor Nerve Palsy
PCA ..... Posterior Cerebral Artery
PComA ... Posterior Communicating Artery
RSR..... Relative Survival Ratio
SAH..... Subarachnoid Hemorrhage
SCA ..... Superior Cerebellar Artery
SIRS..... Systemic Inflammatory Response Syndrome
TOF ..... Time-of-Flight
UCAS..... Unruptured Cerebral Aneurysm Study
UTI ..... Urinary Tract Infection
VIF..... Variance Inflation Factor
WEB..... Woven EndoBridge device
WFNS .... World Federation of Neurosurgical Societies (scale)

Abstract

Introduction

Aneurysmal subarachnoid hemorrhage (aSAH) is a serious form of stroke, caused by a ruptured intracranial aneurysm, that often strikes at the working age. The origin of the posterior communicating artery (PComA) is one of the most common locations for ruptured aneurysms causing aSAH. There are specific features related to the risk of rupture, severity of bleeding and occlusive treatment of PComA aneurysms, identified in few previous studies.

It has been believed that after successful rehabilitation aSAH patients should have a similar life-expectancy to that of the general population. However, lately there have been indications of excess mortality in the long run, at least among some aSAH patient groups.

The aims of this work are 1) to identify the morphological features related to PComA aneurysms and their rupture, 2) to study the treatment and outcome after PComA aneurysm rupture and aSAH, 3) to discover if there is long-term excess mortality after aSAH compared to the general population.

Patients and Methods

Each publication includes a subgroup of 7 289 patients with intracranial aneurysms treated in Helsinki University Hospital between 1980 and 2014. The computed tomography angiography analysis on PComA aneurysm morphology was based on images of 391 PComA aneurysm patients; the treatment and outcome was evaluated in 620 patients with ruptured PComA aneurysm and long-term excess mortality was evaluated after long-term follow-up of 3 078 aSAH one-year survivors.

Results

The most marked morphological features of the PComA aneurysms were saccular nature (99%), inferoposterior dome orientation (42%), infrequency of large or giant aneurysms (4%), narrow neck compared to the aneurysm size, PComA originating directly from the aneurysm neck or the dome (28%), and fetal or dominant PComA on the side of the aneurysm (35%). A significant propor-

tion (38%) of PComA aneurysms ruptured at small sizes (<7mm), and there were location-related parameters that were associated with rupture, highest odds of rupture related to irregular aneurysm dome.

Most of the patients made a good recovery at 1 year after PComA aneurysm rupture and aSAH (62%). A small proportion of patients were left severely disabled (4%). Of all, 20% died during the first year. The risk factors for impaired outcome were poor preoperative clinical condition, intracerebral or subdural hematoma due to aneurysm rupture, age over 65, artery occlusion in postoperative angiography, occlusive treatment-related ischemia, delayed cerebral vasospasm and hydrocephalus requiring a shunt.

There was long-term excess mortality after aSAH compared to matched general population even among young patients and patients who recovered well initially. The highest excess mortality was among patients with multiple aneurysms, old age, poor preoperative clinical condition, conservative aneurysm treatment, and unfavorable clinical outcome at 1 year.

Conclusions

PComA aneurysms rupture also at small sizes, and there are location-related morphological parameters associated with the rupture: irregularity of the aneurysm dome, wider aneurysm neck and aspect ratio >1.5.

Even though most treated aSAH patients recover well after PComA aneurysm rupture, there are occlusive treatment-related complications like artery occlusions and treatment-related brain infarctions causing impaired outcome irrespective of the treatment method. PComA aneurysms may have been seen as fairly uncomplicated lesions, but occlusive treatment of a ruptured PComA aneurysm seems to be a high-risk procedure even in a high-volume neurosurgical center. Some of the complications can possibly be avoided as the variety of treatment modalities increases.

There is excess mortality after aSAH among patients with all aneurysm locations in a long-term follow-up. Cardiovascular events at younger ages and cerebrovascular causes were overrepresented as causes of death. Treatment of vascular risk factors is important after aSAH. Certain patient groups require long-term follow-up.

Tiivistelmä

Johdanto

Lukinkalvonalainen verenvuoto (SAV) aivovaltimopullistumasta eli aneurysmasta on vakava aivoverenkiertohäiriö, johon sairastuvat usein työikäiset. Takimmaisen yhdysvaltimon haarautumiskohta on yksi yleisimmistä sijainneista vuodon aiheuttaneelle aneurysmalle. Takimmaisen yhdysvaltimon aneurysman aiheuttamaan SAV:oon sekä näiden aneurysmien hoitoon liittyy juuri tälle sijainnille tyypillisiä haasteita. Julkaisuja aiheesta on vielä melko vähän.

Aiemmin on ajateltu, että onnistuneen kuntoutumisen jälkeen SAV-potilaiden elinajanodote on vastaava kuin normaaliväestöllä. Viimeaikaiset tutkimustulokset ovat kuitenkin antaneet viitteitä siitä, että SAV:sta toipuneilla, tai ainakin osalla heistä, saattaa olla ylikuolleisuutta suhteessa normaaliväestöön.

Tutkimuksemme tavoitteita ovat: 1) tutkia morfologisia piirteitä, jotka liittyvät takimmaisen yhdysvaltimon aneurysmiin sekä niiden aiheuttamaan verenvuotoon, 2) raportoida hoidon tulokset sekä mahdolliset toipumista heikentävät seikat takimmaisen yhdysvaltimon aneurysman puhkeamisesta seuranneen SAV:n jälkeen sekä 3) ottaa selvää, esiintyykö SAV :n jälkeen ylikuolleisuutta suhteessa normaaliväestöön.

Metodit

Jokainen julkaisu sisältää alaryhmän 7 289 potilaasta, jotka on hoidettu vuotaneen tai vuotamattoman aivovaltimopullistuman vuoksi Helsingin seudun yliopistollisessa keskussairaalassa vuosina 1980–2014. Tietokonetomografiakuviin pohjautuva morfologinen analyysi perustui 391 hoidetun tai seuratun potilaan kuviin; hoidon ja toipumisen suhteen arvioitiin 620 potilasta, jotka oli hoidettu takimmaisen yhdysvaltimon aneurysman puhkeamisesta seuranneen

SAV:n vuoksi; ja ylikuolleisuutta arvioitiin 3 078 SAV:sta selviytyneen potilaan pitkäaikaisseurannan perusteella.

Tulokset

Takimmaisen yhdysvaltimon aneurysman tyyppipiirteitä olivat sakkulaarisuus (99%), suuntautuminen alaviistoon ja taaksepäin sisemmästä kaulavaltimosta, suurten tai jättianeurysmien vähäisyys (4%), kapea kaula suhteessa aneurysman kokoon, takimmaisen yhdysvaltimon lähtökohta tiiviisti aneursman tyvessä tai sen kyljessä (28%) sekä kliinisesti merkittävä fetaali tai dominantti kehityksellinen variantti takimmaisesta yhdysvaltimosta aneurysmaan liittyen oli tavallinen (35%). Takimmaisen yhdysvaltimon aneurysmat vuosivat usein myös pienikokoisina (38% <7mm), ja löysimme tälle sijainnille tyypillisiä aneurysman piirteitä, jotka erityisesti liittyivät vuotoon. Näistä merkittävin oli aneuryman röpelöisyys.

Suurin osa potilaista, jotka olivat sairastaneet SAV:n takimmaisen yhdysvaltimon aneurysman puhkamisen seurauksena, toipuivat hyvin vuoden kuluessa (62%). Vain pieni osa potilaista jäi vaikeasti vammautuneeksi (4%). Hoidetuista joka viides menehtyi ensimmäisen vuoden kuluessa. Riskitekijöitä heikommalle toipumiselle olivat huono leikkausta edeltävä kunto, aivokudoksensisäinen tai kovakalvonalainen verenvuoto SAV:oon liittyen, yli 65 vuoden ikä, aivovaltimon tukkeuma nähtävissä kontrollikuvaksessa, aneurysman hoitoon liittyvä iskeeminen komplikaatio, viiveellä ilmenevä oireinen aivovaltimoiden spasmi tai vuodon jälkeinen vesipäisyys (hydrokefalus), joka vaati pysyvän aivokammiosuntin.

Totesimme SAV:n sairastaneilla ylikuolleisuutta pitkässä seurannassa suhteessa normaaliväestöön, myös nuorten potilaiden sekä hyvin toipuneiden keskuudessa. Ylikuolleisuus korostui potilailla, joilla oli useita aneurysmia, iäkkäillä, ennen hoitoa huonokuntoisilla, konservatiivisesti hoidetuilla sekä niillä, joiden toipuminen oli heikkoa vuoden kohdalla sairastumisesta.

Johtopäätökset

Takimmaisen yhdysvaltimon aneurysmat vuotavat usein pieninäkin, ja havaitsimme morfologisia piirteitä, jotka erityisesti liittyivät vuotoon: aneurysman pinnan röpelöisyys, leveä kaula sekä aneurysman pitkulaisuus (pituus suhteessa kaulan leveyteen >1.5).

Vaikka suurin osa hoidetuista potilaista toipuu varsin hyvin takimmaisen yhdysvaltimon aneurysmavuodon jälkeen, aneurysman hoitoon liittyy haasteita, kuten aivovaltimon tukkeumia sekä aivoinfarkteja, jotka heikentävät toipumista. Näitä esiintyi kaikissa hoitomuodossa. Takimmaisen yhdysvaltimon aneurysmien hoito on nähty melko mutkattomana, mutta se vaikuttaa riskialttiilta toimenpiteeltä jopa aneurysmia paljon hoitavassa neurokirurgisessa yksikössä. Hoitovaihtoehtojen lisääntyessä osa komplikaatioista voitaneen välttää.

SAV:sta toipuneilla potilailla esiintyy ylikuolleisuutta suhteessa normaaliväestöön pitkäaikaisseurannassa. Sydän- ja verisuonisairaudet nuorella iällä sekä aivoverisuonisairaudet korostuivat kuolinsyinä. Verisuonisairauksien riskitekijöiden hoito on erityisen tärkeää SAV:n jälkeen. Tietyt potilaat vaativat myös tehostettua seurantaa.

Introduction

Aneurysmal subarachnoid hemorrhage (aSAH) is a serious disease caused by a ruptured intracranial aneurysm. It is related to high, early case-fatality rate (23–50%), despite better diagnostic tools and improved medical and surgical treatment strategies [104, 260, 201, 196, 64, 75, 121]. Half of the aSAH patients are younger than 55 years [104, 74], and even though only 5–10% of all strokes are caused by subarachnoid hemorrhage, the loss of productive life years is similar to that for cerebral infarction or intracerebral hemorrhage [64, 121].

The origin of the posterior communicating artery (PComA) is the third most common location for intracranial aneurysms [70, 37, 78, 142]. When ruptured, PComA aneurysms cause subarachnoid hemorrhage, but a growing number of aneurysms are found unruptured as the use of imagining studies increases. Even though posterior communicating artery (PComA) aneurysms are encountered frequently in neurosurgical centers, there are a limited number of publications on these aneurysms, and most of them are based on small patient series (n=9-174) [22, 174, 73, 102, 173, 251, 276, 278].

The aSAH strikes unexpectedly, and the treatment and rehabilitation periods are intensive and long. Earlier, it was expected that if the patients recovered well after the initial treatment period, their life-expectancy would be the same as the life-expectancy of the general population. There have been only few publications on long-term survival of aSAH patients and their conclusions have been slightly contradictory [200, 226, 162, 110, 268]. ❦

Review of the literature

25

Aneurysmal Subarachnoid Hemorrhage
Posterior Communicating Artery Aneurysms
And Long-Term Excess Mortality

Aneurysmal Subarachnoid Hemorrhage (aSAH)

Definition

Intracranial hemorrhage caused by a ruptured cerebral or intracranial aneurysm is called aneurysmal subarachnoid hemorrhage (Figure 1). Cerebral aneurysms are pouch-like abnormalities at the wall and branching sites of intracranial arteries. They are often located close to the base of the skull. The aneurysm rupture causes extravasation of blood into the subarachnoid space between pial and arachnoid membranes, usually filled with cerebrospinal fluid, surrounding the brain. At times, there are intracerebral, intraventricular or subdural hematomas related to aSAH [260, 77, 197, 51].

Epidemiology and Risk Factors

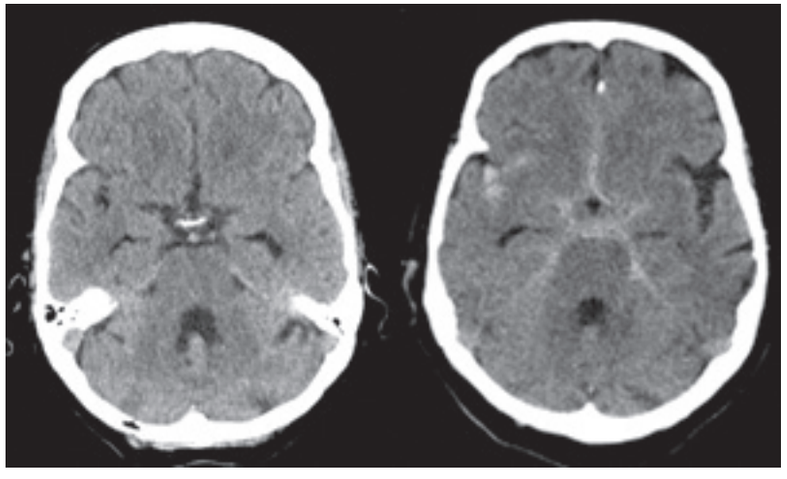
The aSAH patients are often adults at working-age. The mean age at the time of aSAH is about 55 [104, 74]. The disease affects both genders, however, women who smoke seem to have the highest lifetime-risk for aSAH [140]. Other risk factors include high blood pressure, previous smoking, high alcohol consumption, previous myocardial infarction, elevated cholesterol levels in men and family history of aSAH [115, 217, 148, 144]. The risk of aSAH is highest among heavy-smoking women [167].

For decades, there has been a perception that the incidence of aSAH is higher in Finland and in Japan than in other countries in Western Europe and North America [233, 169, 260]. Recently, there is data supporting the idea that the aSAH incidence in Finland is similar to other Nordic countries, about 9/100 000 [143]. The incidence of aSAH has been decreasing, which might be related to decrease in smoking rates [143].

Clinical Symptoms

Typical clinical symptoms of aSAH are an explosive, unusually intense headache, which is often related to nausea, vomiting, confusion and decreased level of consciousness [222]. A sudden comatose state may also be the first symptom of this disease, and a group of aSAH patients (12–25%) die outside of hospital before reaching medical care [235, 143]. Aneurysmal subarachnoid hemorrhage is a severe form of stroke. For these patients, fast medical attention is important.

Figure 1
Axial CT images of the patient with a normal scan (on the left) and the patient with subarachnoid hemorrhage in the basal cisterns (on the right).



Systemic, cardiovascular and hormonal effects are related to first days and weeks after aSAH [36, 76, 28, 230, 81, 11]. Even after the initial state, neurological deficits, confusion, memory defects and other neuropsychological symptoms are common [94, 13, 208, 215, 214].

Diagnosis of aSAH

When a patient is symptomatic and aSAH is suspected, the diagnosis is based on imaging studies. Computed tomography (CT) scan usually reveals blood in the subarachnoid space. In selective cases, for example in delayed diagnosis, a lumbar puncture might be needed to confirm the subarachnoid hemorrhage [260, 91].

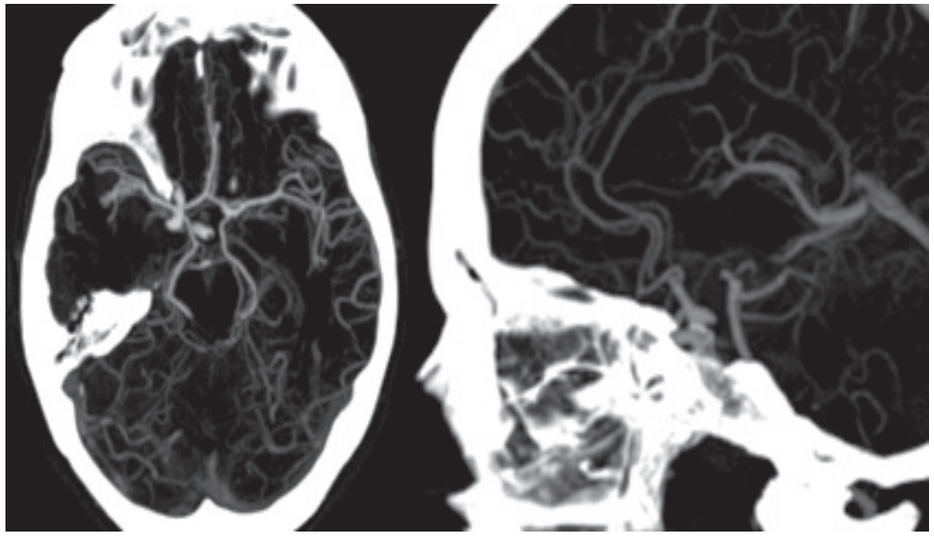
Computed tomography angiography (CTA) is nowadays the fastest first-line non-invasive method in detecting ruptured intracranial aneurysms (Figure 2) [127, 270, 128, 263, 273]. Sensitivity and specificity of CTA are high (>95%), and the images are often sufficient for treatment planning [270, 263]. CTA images nowadays enable the creation of high-quality 3D-image reconstructions. In emergency situations, CTA is preferred as a fast and reliable diagnostic tool. In complex aneurysms, digital subtraction angiography (DSA) is the preferred method for imaging. In finalizing an endovascular treatment plan, the DSA is routine [205, 128, 106].

Complications of aSAH

Rebleeding

The peak incidence of rebleeding occurs within 24 hours and remains high during the first week after the initial bleeding [124, 112, 252]. There is high mortality related to rebleedings [124, 248, 100]. The early rebleeding rate seems to be higher the more severe the initial bleeding is [112, 252]. The goal of the occlusive aneurysm treatment is to prevent re-

Figure 2
Axial and sagittal CTA images on intracranial arteries, 2-D reconstructions.



current hemorrhage. Nowadays, it is recommended to treat the ruptured aneurysm as early as feasible after the initial bleeding [36]. The ultra-early rebleedings are still a challenge. Treatments such as bed rest, antihypertensive drugs, antifibrinolytics and sedatives are being used in attempts to prevent early recurrent hemorrhage [49, 99, 93, 245, 36, 113].

Delayed Cerebral Ischemia

Delayed cerebral ischemia (DCI) has been classically contributed to cerebral vasospasm, which describes unwanted constriction of the intracranial arteries, a state that can strike during the first two to three weeks after the aSAH (Figure 3) [39]. It can lead to cerebral infarctions and have an impairing effect on outcome of aSAH patients [65, 39, 74, 36, 260, 53]. About one third of aSAH patients suffer from symptomatic vasospasm after aneurysmal subarachnoid hemorrhage. Nearly twice as many have radiological vasospasm [179, 53]. The whole pathogenesis of delayed cerebral ischemia is not yet understood, and improvement in radiological vasospasm does not clearly correlate with improved functional outcomes [147, 178]. There is increasing evidence of co-existing factors, and nowadays, delayed cerebral ischemia is thought to be a combined result of delayed vasospasm, arteriolar constriction, thrombosis and dysfunction in microcirculation and cortical spreading ischemia [65, 259, 39, 236, 207, 53, 69, 55]. These changes are triggered by the early brain injury caused by aSAH.

Earlier, the triple-H-therapy (hypervolemia, hypertension, hemodilution) was routinely used for prophylaxis and treatment of this condition. Later, several publications have shown that hypervolemia and hemodilution do not seem to be beneficial on cerebral blood flow and oxygenation and are

Figure 3
Axial postoperative CTA images with normal intracranial arteries (on the left) and after symptomatic vasospasm and radiological caliber changes in the intracranial arteries (on the right).

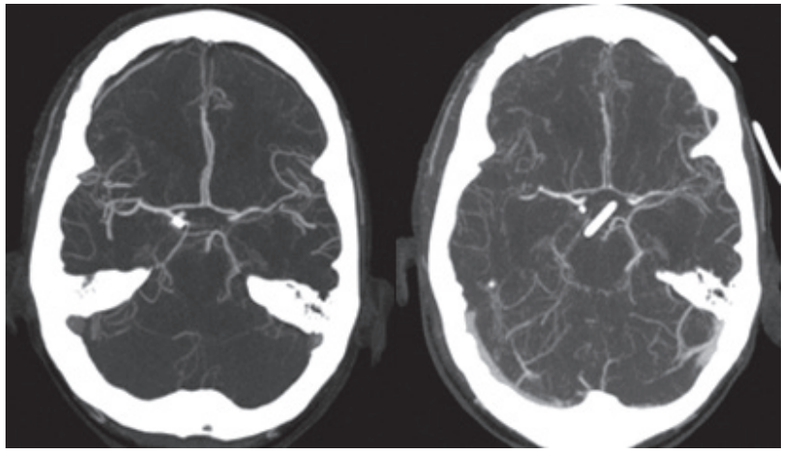
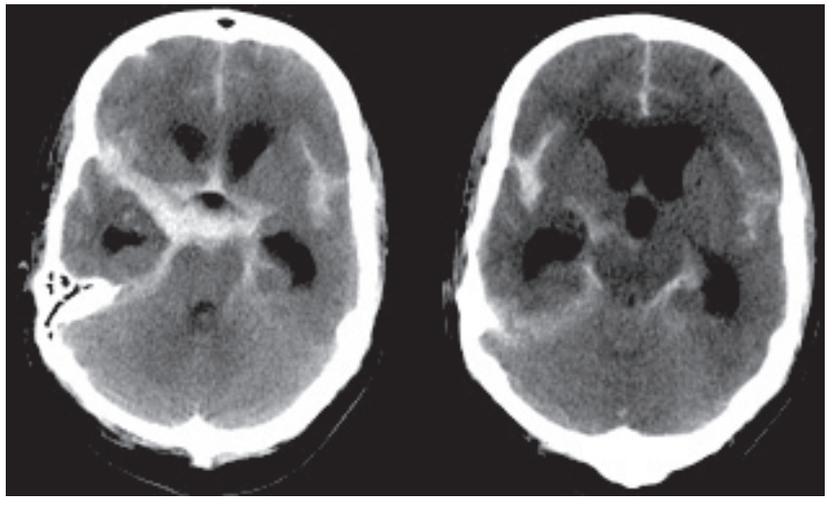


Figure 4
Axial CT scans showing subarachnoid hemorrhage and hydrocephalus (enlargement of the ventricles).



therefore not recommended [49, 10, 218, 190, 164, 59]. Induced moderate hypertension and normovolemia are often sufficient for improving brain tissue oxygenation, and they have lower complication rates than hypervolemia and aggressive hypertension. At times, increasing the cardiac output in addition to blood pressure elevation may be needed as a part of hyperdynamic therapy. The use of calcium-channel blockers is a part of the prophylaxis and treatment protocol, and they seem to have beneficial, neuroprotective properties even though there is no radiological effect on vessel vasodilatation [49, 218, 190, 10, 53, 209, 246]. Intra-arterial vasodilator therapy and balloon angioplasty have been used in many neurosurgical centers as endovascular rescue therapy for severe symptomatic vasospasm, but in addition to promising benefits, there are also challenges such as the need for repeated procedures and a risk of severe complications that need to be considered. Presently, there is insufficient data to support a systematic use of these endovascular rescue therapies. Selected patients with symptomatic vasospasm noncompliant to conventional treatment may be candidates for this [97, 49].

Although there are promising results indicating that with modern treatment, delayed cerebral vasospasm might not increase in-hospital mortality in aSAH patients [154], there is still a significant proportion of patients with poor response to treatment and increased morbidity because of this condition [65, 179, 53, 74]. In spite of on-going research and efforts, the main therapeutic interventions remain quite ineffective in preventing morbidity [84].

Hydrocephalus

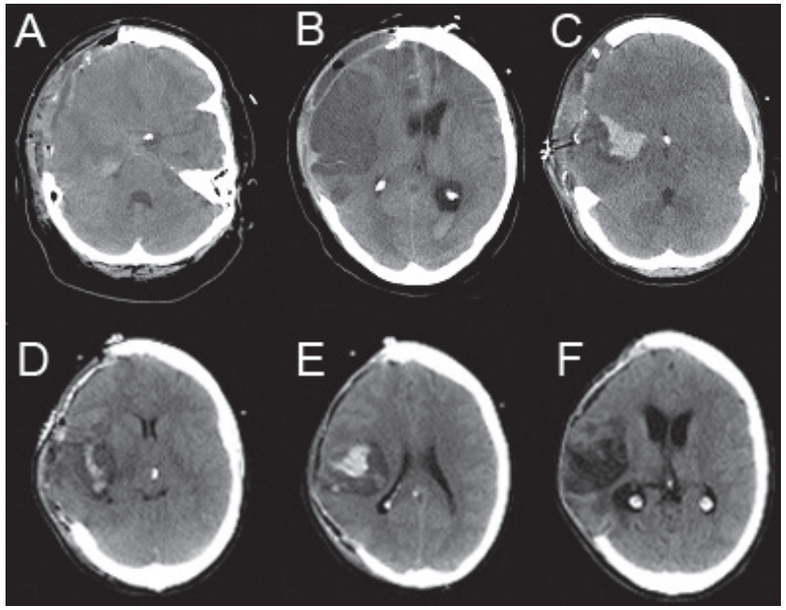
Subarachnoid hemorrhage can disrupt the normal flow of cerebrospinal fluid [82]. Hydrocephalus is a clinical manifestation of this disruption (Figure 4). There are indications that intraventricular hemorrhage, older age, acute hydrocephalus on admission and the need for external ventricular drainage (EVD), poor clinical condition and meningitis are factors that increase the risk of chronic post-SAH hydrocephalus and need for permanent shunt to treat the condition [240, 1]. A gradual EVD weaning may decrease the risk of shunt dependency, but there are still only few publications and controversial results on the subject [117, 136, 32, 80]. About one fifth of the treated aSAH patients need a shunt after the aSAH (18–26%); chronic hydrocephalus is related to significant morbidity and re-admissions to hospital [52, 1, 109, 280, 85].

Others

Systemic Complications

Subarachnoid hemorrhage causes both cerebral and extracerebral complications. Many systemic effects could primarily be due to sympathetic nervous system activation. Additionally, they may be related to the systemic inflammatory response syndrome (SIRS), which may occur due to cerebral interleukin release or through catecholamines promoting immune activation [76]. Systemic complications include neurogenic pulmonary edema, electrocardiographic (EKG) changes, neurogenic stunned myocardium, hyponatremia and anemia [231, 160, 191, 76, 36, 28, 230, 81, 11]. They are typically related to early post- aSAH stage. Critically ill patients are also prone to problems like infections and thromboembolic complications. The recognition and treatment as well as prevention of these complications have a great impact on the outcome of aSAH patients.

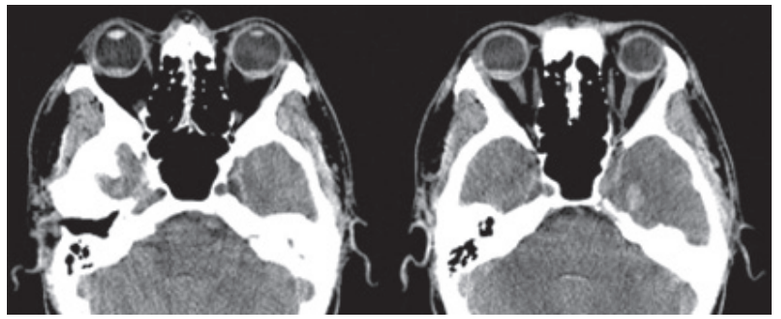
Figure 5
Axial CT images after decompressive hemicraniectomy to treat refractory intracranial hypertension caused by A-B) severe vasospasm and large right-sided ACA and MCA area infarctions or C-E) intracerebral hemorrhage and odema. F) Sequelae of the hemicraniectomy and resorption of the intracerebral hemorrhage.



Other Cerebral Complications

There have been two patterns of elevated intracranial pressure (ICP) described: transitory and sustained. The latter is associated with severe reduction in cerebral blood flow, cerebral perfusion pressure and impaired cerebral autoregulation [39]. One issue under debate in the treatment of cerebral complications after aSAH is the role of decompressive craniectomy as a rescue therapy for refractory intracranial hypertension or sustained elevated ICP (Figure 5). A recent meta-analysis on this issue pooled a rate of 61% for poor outcome and 28% for death at a median of 12 months after aSAH [5]. There are only observational studies on this difficult clinical scenario, and randomized trials might yield more valuable information. So far, however, a moderate or reserved attitude towards this surgical therapy might be supported by the published data. Also, the cranioplasty operation needed after decompressive craniectomy is related to quite frequent complications. These include most often wound healing disorders, bone necrosis, hygromas or postoperative epidural hematomas causing the need for several operations [264]. In the end, individual evaluation is essential.

Figure 6
Terson syndrome e.g. vitreous bleeding related to aSAH may be seen in the axial CT scans.



Neuro-Ophthalmic Symptoms

The most common neuro-ophthalmic condition related to aSAH is the Terson syndrome, a vitreous bleeding impairing the vision, with an incidence of close to 20% in aSAH patients (17–19%, Figure 6). Its incidence is often underestimated, or it is left undetected due to the impaired clinical condition of the patient or due to the inability of the patient to communicate adequately. The Terson syndrome is associated with poor clinical condition on admission, and thus, it should be ruled out in patients presenting comatose or with signs of raised ICP [42, 122, 247].

Other neuro-ophthalmic symptoms include third, fourth or sixth nerve palsies, which may be present in about every tenth aSAH patient pre- or postoperatively [145]. They may be related to nerve injury caused by the bleeding, the compression of the nerve by the aneurysm or manipulation of the nerve during the operation. Most of these symptoms resolve spontaneously. About 3% of treated patients have partial palsy at 1 year after treatment [146]. The most commonly recognized neuro-ophthalmic symptom is the third nerve palsy or oculomotor nerve palsy associated with posterior communicating artery aneurysms. Compression of the isolated cranial nerves, such as fourth, fifth and sixth nerves within the cavernous sinus is a less common but another typical site for causing deficits. Cranial nerve palsies may, however, be associated with other aneurysm locations as well. Horizontal gaze pareses and Parinaud´s syndrome may also exist, but they are rare [105, 12, 146].

Treatment of aSAH

The aims of the treatment of aSAH patients are a) to stabilize hemodynamics and ventilation as well as neurological and systemic effects after the bleeding b) to secure the patient from the risk of rebleeding c) to offer a change of recovery after the early brain injury caused by the initial bleeding and d) to prevent and treat any potential delayed complications related to aSAH. Active treatment includes all of the goals above, but it is often used as a term to refer to the goal to exclude the ruptured aneurysm from the intracranial circulation. Historically, the active or occlusive aneurysm treatment has been the center of focus in neurosurgical treatment. The techniques to achieve this goal are varied.

Table 1
Landmarks in aneurysm surgery, focus on diagnostics and treatment.
[213, 35, 29, 20, 182, 202, 171, 7, 72, 161, 193, 67, 261, 249]

Year	Innovation	Performed by
1805 – 09	Carotid ligation	Cooper, Hunter, Travers
1885	Carotid ligation for treating an intracranial aneurysm	Horsley
1891	Lumbar puncture	Quincke
1911	Compression test and carotid occlusion clamps	Matas
1911	Cushing´s silver clip	Cushing
1917	Recommendation to use local anesthesia for all neurosurgical operations	Cushing
1921	1st surgical monocular microscope	Nylen
1926	Bipolar cautery	Bovie/Cushing
1927	Flat silver wire clip	McKenzie
1927	Cerebral angiography	Moniz
1931	Wrapping an aneurysm with muscle	Dott, Norman, McCormick
1932	Trapping an intracranial aneurysm	Olivecrona
1933	Ligations of the neck of aneurysm	Dott, Jefferson
1936	Percutaneous ICA puncture technique in angio	Myerson, Lowman
1937	Clipping an intracranial aneurysm	Dandy
1939	Wiring of intracranial aneurysm	Blakemoor
1940	Bipolar forceps	Greenwood
1945	Extracranial ligation of vertebral artery for vertebro-basilar aneurysm	Dandy
1949	Complete (four-vessel) angiography	Raney, Anchez-Perez
1050´s	Externally adjustable clamps for carotid occlusion	Selvestone, Crutchfield
1951	First demonstration of cerebral vasospasm	Ecker, Riemenschneider
1952	Cross-legged clip for aneurysm surgery	Mayfield, Kees
1953	Percutaneous transfemoralis puncture technique in angio	Seldinger
1954	Neuroanesthesiolocigal advances: hyperventilation, osmotic agents	Javid
1957	1st Neurosurgeon to use operating microscope	Kurze
1967	STA-MCA-bypass	Yasargil
1970´s	Development of versatile clips for aneurysm surgery	Kees, Drake, Mayfield, Sundt, McFadden, Schwartz, Fox, Yasargil, Sugita
1974	Endovascular use of catheter and silicon substance	Serbinenko
1977	1st titanium clip	Steiner
1986	Microcatheter and microguidewire	
1990	Detachable coils	Guglielmi
1990 –	Mini-invasive approaches in microsurgery	Perneczky, Hernesniemi, Nathal, Fischer
2004	Stents / Flow diversion	Barath

Historical Aspects
In the early 20th century, bed rest was the main treatment offered to aSAH patients. Only some clinically good grade patients survived, and many died due to rebleeding. The earliest techniques in the treatment of cerebral aneurysms were indirect surgical methods, including common carotid artery occlusion, followed by internal carotid artery occlusion, and muscle-wrapping or trapping of the aneurysm. These early techniques often required sacrificing major arteries and treatment-related mortality was high [202, 213, 171]. The development of modern microsurgery has been very dependent on the development of imaging techniques, neuroanestesia as well as intensive care, and technical advances like the operating microscope, bipolar forceps and suction [29, 213, 202, 171, 20]. Some of the milestones in the history of intracranial aneurysm surgery are presented in table 1.

Microsurgical Treatment of Ruptured Aneurysms
In microsurgical treatment, the ruptured aneurysm is occluded in an open microsurgical operation under general anesthesia and under the operating microscope. A clip or clips (nowadays usually titanium) is placed over the neck of the aneurysm occluding the aneurysm dome and the rupture site. Today, this operation is often done using mini-invasive approach, and the operation plan is always individual. If an aSAH patient has a severe bleeding with large intracerebral hematoma or subdural hematoma, a microsurgical operation offers the possibility of evacuating the hematoma during the operation.

Endovascular Treatment of Ruptured Aneurysms

In endovascular treatment, platinum coils are introduced into the aneurysm dome via a microcatheter which leads to the occlusion of the aneurysm. This operation is called coiling or embolization. The endovascular era dawned in 1990, when Guglielmi introduced his innovation: Guglielmi detachable coils. Since then, the endovascular treatment has steadily gained popularity, and nowadays, it has already surpassed microsurgical treatment as the most widely used method in occlusive treatment of intracranial aneurysms in Western countries [165].

Conservative Treatment

The conservative treatment means that no occlusive treatment for the ruptured aneurysm is attempted. In case of a ruptured aneurysm, the conservative treatment is typically chosen due to very poor clinical condition of the aSAH patient, co-morbidities or old age which would make the active treatment too risky. Usually, these patients are treated in the Intensive Care Unit in ventilators with antihypertensive drugs and painkillers in addition to treating the hydrocephalus and extracranial complications in an attempt to give the patient a chance of clinical improvement. However, if the clinical state of aSAH patient proceeds to brain death, neurosurgeons and neuroanesthesiologists are under obligation to estimate the patient's suitability for organ donation [66, 185, 50]. Aneurysmal subarachnoid hemorrhage has been the most common cause of death in organ donors during the past years in Finland. This means that neurosurgeons have a key role in recognizing the potential donors and in discussing this important but sensitive issue with the families (Figure 7).

Treatment at the Intensive Care Unit

As aSAH patients are critically ill and changes in their clinical state might be unexpected and sudden, the suitable place for their treatment is an intensive care unit with specialized staff, including neurosurgeons, neuroanesthesiologists and neurosurgical nurses. As the disease is complex with potential cerebral and extracerebral complications, it is important that the staff is familiar with the disease in order to be able to recognize and treat the various conditions without delays. After aSAH patients have been stabilized, the neurosurgical nurses monitor the circulation, ventilation and level of consciousness of these patients, and the symptoms are being alleviated. Also, the family of the aSAH patient is informed and supported by the staff.

Rehabilitation

The clinical manifestation and deficits of the patient can vary and the rehabilitation should be planned according to individual needs. For example, physiotherapy might be needed for a paresis of a limb or for problems with gait or balance and a neuro-ophthalmologist might be needed for visual problems. In the presence of neuropsychological symptoms like tiredness, difficulties in memory functions or concentration and vulnerability to be overwhelmed by physical or psychological stress, a multidisciplinary team (including a neurologist, a neuropsychologist, an occupational therapist and a physical therapist) would be recommended in planning the rehabilitation and eventual return to work. These patients seem to have the need for structured support to reduce persisting mood disturbances and to increase independence and participation [94, 95, 13, 208, 88, 181, 215, 214, 23, 56, 57, 206].

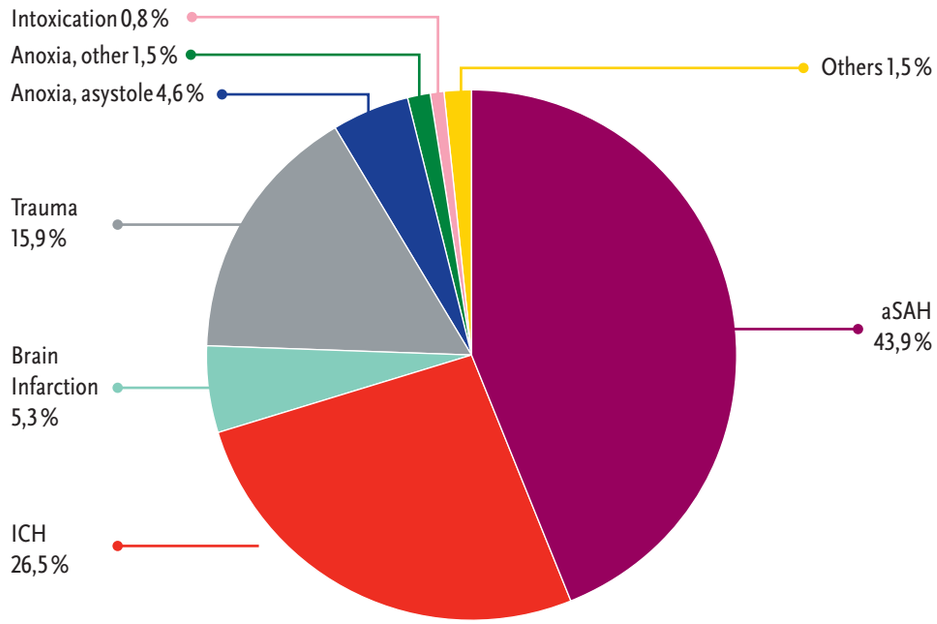
Outcome after aSAH

Case fatality Rate

The early case fatality rate after aSAH is still high (23–50%) despite better diagnostic tools and improved medical and surgical treatment strategies [104, 201, 196, 64, 75, 121]. A review, published ten years ago, showed a 15% decrease in case fatality rates of aSAH during the three previous decades [104]. As a fairly stable proportion, 12 to 25% of aSAH patients die outside hospitals [235, 166] and another 10 to 30% never recover from the severe initial bleeding, only a limited proportion of aSAH patients profit from medical and procedural developments.

Figure 7

Causes of Brain Death of 132 Organ Donors in Finland in 2016.
Data from Transplantation Center, Helsinki University Hospital, Helsinki, Finland;
published with the permission of the Transplantation Center.



ICH: Intracerebral hemorrhage; aSAH: aneurysmal subarachnoid hemorrhage

Outcome and Morbidity

Several studies have reported an early outcome after aSAH, the final follow-up varying from 1 month to 1 year after the aSAH. These previous results report 46–78% of aSAH patient having favourable outcome, 14–23% having significant neurological deficits or morbidity and 8–36% mortality. [186, 234, 237, 98, 2, 262].

A good neurological outcome does not exclude neuropsychological deficits. Even in patients with favourable recovery, problems in concentration and memory, information processing capacity as well as language problems are common [109, 94]. Many aSAH patients suffer from increased mood disturbances, subtle cognitive impairment, and abnormally low independence and participation in social functions [109, 215, 214].

Long-Term Mortality

Previously, the general belief has been that aSAH should have no further effect on patient survival after successful initial recov-

Table 2
Grading systems for aSAH patients according to patient´s clinical condition [108], [254].

Hunt and Hess grade	Description
I	Mild headache or slight nuchal rigidity
I	Mild headache or slight nuchal rigidity
II	Moderate or severe headache, nuchal rigidity or cranial nerve palsy
III	Lethargy, confusion, mild focal neurological deficit
IV	Stupor, early decerebrate rigidity or moderate to severe hemiparesis
V	Deep coma, decerebrate rigidity, moribund appearance

WFNS grade	Glasgow Coma Scale (GCS)	Motor Deficit
I	15	No deficit except a cranial nerve palsy
II	14–13	No deficit except a cranial nerve palsy
III	14–13	Any deficit
IV	12–7	With or without deficits
V	6–3	Coma with or without abnormal posturing

ery. However, a majority of the latest studies have detected long-term excess mortality after aSAH. Some of the results partly contradict each other, especially when it comes to survival of young patients and patients with good initial recovery [226], [268], [110], [141], [187], [195].

A population-based study of 1746 aSAH patients in Eastern Finland showed excess mortality of 12% at 15 years (median follow-up 12 years, cumulative RSR 0.88, 95% CI 0.85–0.91) [110]. A previous Finnish study on 1537 aSAH patients had also reported excess mortality and suggested that aSAH might be a manifestation of a general vascular disease [226]. Yet another Finnish study on 233 one-year aSAH survivors showed excess mortality caused by deadly cerebrovascular events, aSAH and others, in comparison to the general population [141]. A Dutch study also showed an elevated incidence of cerebrovascular and cardiovascular events in aSAH patients [268].

An Icelandic study stated that there was no long-term excess mortality in patients who had made favorable recovery at 6 months [21], whereas Ronkainen et al. reported the excess mortality to be most evident in younger age groups [226]. Also, another Dutch study stated that increased risk of vascular disease and death were pronounced especially in younger patients [195].

Table 3
Two grading systems for patient´s clinical, neurological outcome after aSAH

GOS score	GOS grade	Description
5	Good Recovery	Return to normal functional level and employment
4	Moderate Disability	Minor neurological deficits, still independent in daily living
3	Severe Disability	Need of assistance, significant neurological deficit that interferes with daily activities and prevents return to employment
2	Vegetative	Coma or severe deficits leaving patient totally dependent of others
1	Death	Death

mRS score	mRS grade	Description
0	No symptoms	No symptoms
1	No significant disabilities	Despite symptoms, able to perform all previous activities and employment
2	Slight disability	Unable to perform all previous activities, but able to take care of own affairs without assistance
3	Moderate disability	Requires some help, able to walk without assistance
4	Moderately severe disability	Unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability	Bedridden, incontinent, need for constant care and attention
6	Death	Death

Risk Factors for Impaired Long-Term Outcome

Previous studies have suggested that conservative treatment, older age, male sex, aneurysm location, severe hydrocephalus on admission, impaired clinical outcome at early stage, smoking, hypertension and elevated cholesterol values are factors that may be related to the long-term outcome of aSAH patients [110], [162], [141]. Familial background of aSAH or mode of occlusive therapy have not been considered risk factors 110.

Grading Systems related to aSAH

There are several grading systems that have been regularly used in the research of aSAH patients [227], [152]. In evaluating the patient's initial clinical condition, Hunt & Hess grade (HH grade) and World Federation of Neurosurgical Societies classification (WFNS grade) have been used to describe the severity of clinical symptoms and also as a predictor of patient's outcome, with a higher grade often correlating to a lower survival rate (Table 2) [108], [254].

The Glasgow outcome score (GOS) and the modified Rankin scale (mRS) describe the clinical outcome of a patient at a certain point of follow-up (Table 3) [120], [219]. Also, the severity of bleeding has its own scale, Fisher scale [68], which has been associated with the risk of delayed cerebral vasospasm (Table 4).

It is important to realize that these scales are rough neurological or radiological scales and, for instance, a good neurological outcome according to these scales does not exclude more subtle deficits like neuropsychological deficits that can have serious effects on the everyday life of these patients. Still, these scales offer a useful tool to group different risk groups among the diverse aSAH patients [227], [152], [10], [25].

Table 4
Fisher scale describes the severity of aSAH according to radiological evaluation.

Fischer scale grade	Explanation
I	No blood
II	Diffuse, thin (<1mm) a SAH
III	Layers of blood >1mm in thickness, no IVH
IV	aSAH with any ICH or any IVH

Unruptured Intracranial Aneurysms

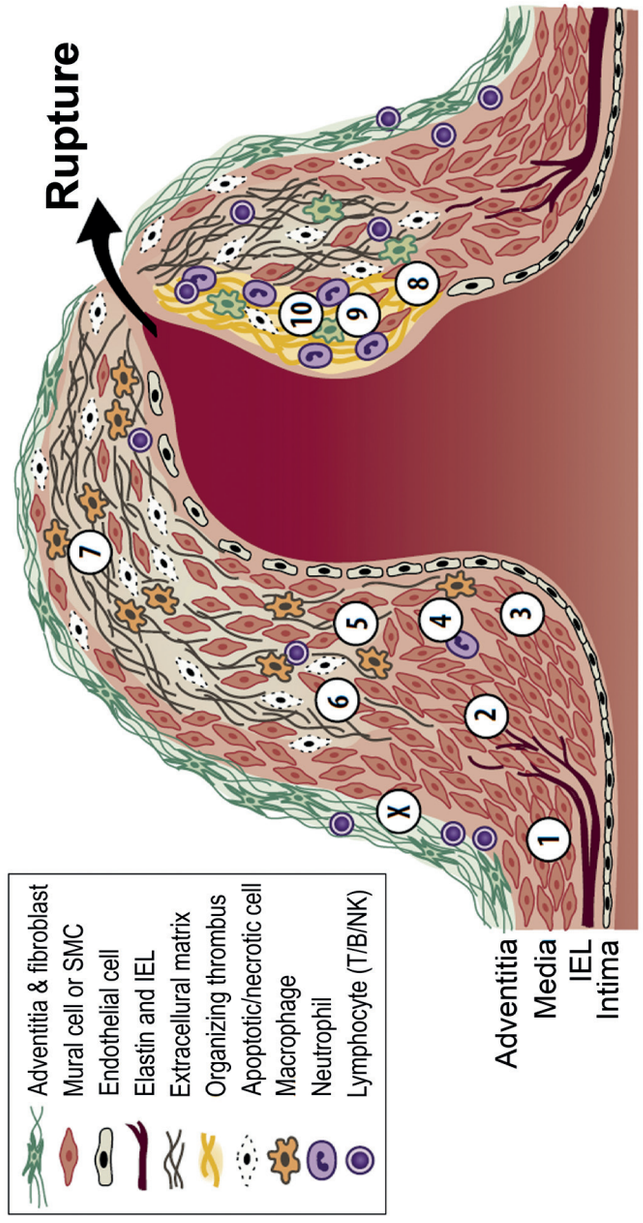
Epidemiology

Unruptured intracranial aneurysms are quite common. It has been estimated that 2% of the population, meaning about 100 000 Finns, carry an unruptured intracranial aneurysm. The risk tends to increase with age. Most of the unruptured aneurysms are sporadic and never cause any symptoms. The prevalence of intracranial aneurysms seems to be higher in patients with polycystic kidney disease, familial background of aSAH or atherosclerosis [223], [138], [260].

Aneurysm Wall Pathology

Intracranial aneurysms seem to develop in the course of time [223]. We do not fully understand the process of aneurysm formation and rupture. It has been assumed that aneurysms form as a result of an interplay between hemodynamic factors and structural weaknesses at the wall of arterial bifurcations. Hypertension, smoking and time seem to help the formation. A disruption of the internal elastic lamina of the arterial wall seems to be an essential requirement for formation of a cerebral aneurysm, since this layer provides the most of the strength to the walls [277]. A major rupture is often preceded by inflammatory process, presented in Figure 8, following degenerative reaction

Figure 8
A hypothetical presentation of cerebral aneurysm wall degeneration and rupture. This figure has been originally created by Tulamo et al. 2011 and published by Duodecim [258], and it has been republished with the permission of Duodecim.



An intracranial aneurysm forms as the internal elastic lamina (IEL) gets disrupted (1) together with myointimal hyperplasia (2). Hemodynamic stress leads to endothelial dysfunction (3) and to chemotaxis for inflammatory cell invasion (4). The matrix synthesis is increased due to the function of growth factors (5). Lymphocytes appear at some point (X). Because of the cytotoxic milieu caused by inflammatory cells, by the increased matrix and by decreased oxygen supply inside the thickened wall, the mural cells begin to die (6) leading to slowing in the matrix turnover (7). The aneurysm wall becomes mechanically more fragile. As the intraluminal pressure exceeds the tensile strengths of the wall, it ruptures.
In some aneurysms, depending on hemodynamics and shear stress accompanied with the endothelium dysfunction or death, there is thrombus formation (8). The thrombus attracts neutrophils (9), potent producers of proteolytic enzymes. Over time, the thrombus may become organized by migrating mural cells (10). Caused by cell death and decreased matrix turnover, the aneurysm wall may eventually become sufficiently fragile to rupture.

of the wall, bleb formation, or minor hemorrhage [257, 54, 238]. More angiographic, experimental and clinical studies will be needed to give us better understanding on the issue of aneurysm formation, growth and rupture.

Natural History and Risk of Rupture

The annual risk of aneurysm rupture is about 1% (0.5–1.6%) [223, 140, 272, 188]. The risk is reported to be highest in current smokers, especially in women who smoke. The risk of rupture is increased also for symptomatic aneurysms, for larger aneurysms (>7–10mm) and for posterior circulation aneurysms, as well as for posterior communicating artery aneurysms of the internal carotid artery [223, 186, 272, 188, 140]. Depending on the risk factor burden, the annual rupture rate can vary significantly (0–6.5%) [140]. Approximately 10% of aneurysm patients have a family history of intracranial aneurysms [223].

Imaging

CTA

Conventional cerebral angiography or digital subtraction angiography (DSA) has been regarded as the gold standard for detecting intracranial aneurysms [128, 106]. In last decades in clinical practice it has been challenged by computed tomography angiography (CTA), which is a quick, non-invasive, reliable and relatively simple diagnostic tool with high sensitivity and specificity (>95%) [106, 127, 270, 263, 273]. According to several studies, it seems safe and effective to make the diagnosis of unruptured or ruptured intracranial aneurysm and treatment decisions based on CTA without performing DSA in majority of cases [103, 127, 270, 106, 263, 273]. In both of these imaging studies, radiation exposure as well as potential complications related to the use of iodinated contrast agent must be kept in mind [128].

DSA

Conventional DSA provides detailed information regarding the presence, anatomic location, morphology and flow dynamics of an intracranial aneurysm [260, 128]. DSA images have better resolution than CTA when it comes to smaller vessels, but have restrictions when it comes to less vascularized structures and bony landmarks. In selected cases, for example in aneurysms with challenging morphology, the DSA yields the most valuable information. It is also needed for endovascular treatment planning [205, 128, 106].

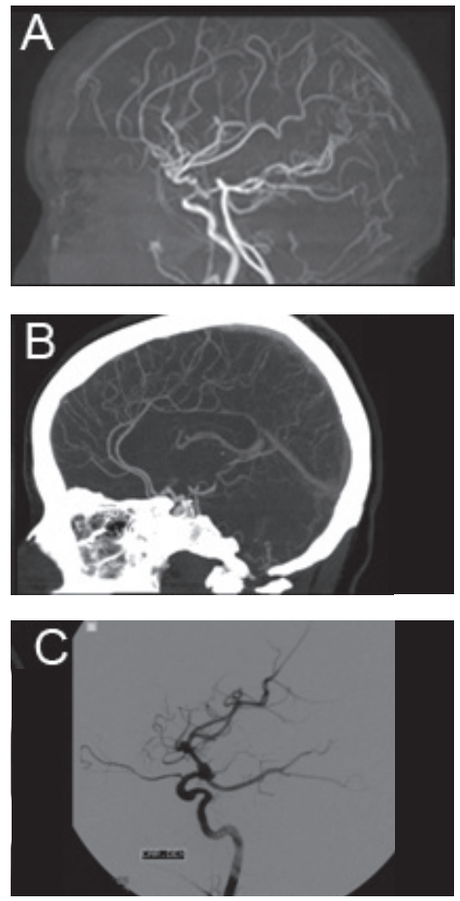
As a diagnostic tool, DSA is invasive and time-consuming and a large amount of contrast material as well as radiation is required. As an invasive method, DSA is associated with low but factual risk of neurological complications (<1%) and minor complications like hematoma, pseudoaneurysm or arteriovenous fistula at the puncture site. Also, allergic reactions or nephrotoxicity from the iodinated contrast agent might cause serious problems [34, 96].

MRA

Magnetic resonance angiography (MRA) is another non-invasive technique for detecting intracranial aneurysms. It does not require radiation exposure. Although its sensitivity has been slightly inferior compared to DSA (Figure 9), it can provide complementary information in anatomically complex areas, or in the presence of intramural thrombus [128, 3, 228, 83, 14]. MRA has an overall sensitivity of 93–97% in detecting aneurysms larger than 3mm, and about 85–93% in detecting very small, <3mm aneurysms [128]. As with other techniques, a meticulous, standardized imaging technique is important, and multiplanar reconstructions and 3-D reconstructions are valuable [3]. The image interpreter must have sufficient experience [199].

In addition to detecting intracranial aneurysms, MRA have also been used after initial postoperative DSA controls in the long-term follow-up of patients with coiled aneurysms. Pooled sensitivity and specificity for detecting residual flow have been approximately 85% and 90% respectively for both time-of-flight (TOF) and contrast-enhanced (CE) images [150, 41, 4].

Figure 9
Sagittal 2-D images of intracranial arteries in A) MRA, B) CTA and C) right carotid DSA angiographies.



Prophylactic Treatment of Unruptured Aneurysms

The goal of the prophylactic treatment of unruptured intracranial aneurysms is to exclude the aneurysm from the normal circulation in order to minimize the risk of rupture and potentially lethal hemorrhage. The goal is also to do this without causing any harm to the patient. Unfortunately, this is not always possible and the prophylactic treatment is related to the risk of morbidity (3–10%), and even a small risk of mortality (0–3%) [114 272].

One problem is the difficulty of predicting which unruptured aneurysms are going to rupture. We try to estimate the risk of rupture using the known natural history of intracranial aneurysms and the known risk factors for rupture, taking into consideration the patient´s life-expectancy and the risks of prophylactic treatment. There are treatment scores, like aneurysm rupture risk score (PHASES) and unruptured intracranial aneurysm treatment score (UIATS), which can be used as a clinical application for aid in treatment decisions on incidental intracranial aneurysms [86, 62]. All the factors are pooled together in an attempt to estimate which is a greater risk for the patient in a long run, the potential risk and effects of the aneurysm rupture or the potential risks related to the prophylactic treatment of an unruptured aneurysm.

Decision-Making in Treatment of Unruptured Aneurysms

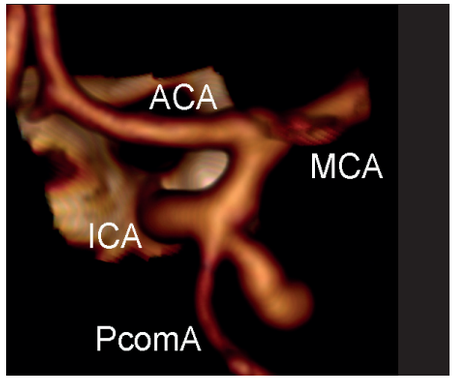
The detailed treatment plan is based on multiple patient and aneurysm-related factors like the size of the unruptured aneurysm, the location of the aneurysm, the risk factors for aneurysm rupture, the age and sex of the patient, other co-morbidities and life expectancy as well as the risk of complications related to the treatment. Also, the experience of the treating physician and the treatment unit are relevant [114, 272, 188, 140, 86, 62, 243].

Of the aneurysm-related factors, the size of the aneurysm is one of the most significant parameters in decision-making. Larger aneurysms usually have a greater risk of rupture, whereas very small aneurysms (1-3mm) seem to have minimal risk of bleeding [125, 188, 192, 267, 272, 123]. According to prospective multicenter cohort studies ISUIA and UCAS, there has been discussion if small unruptured aneurysms of anterior circulation (<7mm) should be treated at all, bearing in mind their minimal risk of rupture. This is still controversial, because when looking at consecutive patient series, they have a notable proportion of patients with small, ruptured aneurysms [225, 138]. After all, an individual estimation and risk assessment is crucial.

The risks of occlusive aneurysm treatment increase substantially after the age of 60–70 years. In addition to older age, other predictors of potentially poor surgical outcome include larger aneurysm size, location in the posterior circulation and a history of cerebrovascular disease [189, 272]. Endovascular morbidity and mortality may be less dependent on the patient´s age [272]. One problem is that quite often a high-risk natural history of an aneurysm is associated with a high surgical risk for the patient.

Finally, decision-making is not solely about balancing the risks of aneurysm rupture and the risks of treatment. After receiving adequate information, the patients themselves have to make the final decision regarding their own health. Often, this decision is made together with the treating neurosurgeon after the consultation of the neurovascular team. Unfortunately, it is impossible to predict in detail which risks – risks of the disease or of the treatment – are going to manifest in the case of a single individual.

Figure 10
PComA aneurysms originate from the internal carotid artery at the origin of the posterior communicating artery.



Posterior Communicating Artery Aneurysms

Definition

The posterior communicating artery (PComA) aneurysms are located along the internal carotid artery (ICA) at the branching site of the posterior communicating artery (Figure 10). The origin of the posterior communicating artery is the most common site for aneurysm formation on the ICA [275].

Epidemiology

The origin of the PComA is the third most common of all locations for ruptured intracranial aneurysms following middle cerebral and anterior communicating arteries. Depending on the series, 13–25% of all ruptured intracranial aneurysms are PComA aneurysms. For unruptured PComA aneurysms, the proportion is a bit lower [70, 186, 37, 78, 142, 250].

Clinical Presentation

A majority of cerebral aneurysms, including PComA aneurysms, are still detected after acute onset of subarachnoid hemorrhage [276]. According to previous studies, 19–38% of PComA aneurysm patients, ruptured or unruptured, present with a unilateral oculomotor nerve palsy (ONP). This condition usually includes ptosis, mydriasis or extraocular muscle weakness and it can be partial or complete [159, 242]. Some patients have accompanying headaches or orbital pain related to ONP [155, 9].

As availability and use of cerebral imaging, especially MR and CT imaging, increases, there will be a growing number of intracranial aneurysms as incidental findings. Some studies have reported 2 to 4% of patients going through imaging studies (stroke patients or healthy controls) having incidental intracranial aneurysms [116, 133].

2.3.4. PComA Aneurysms and the Rupture Risk

It seems that the size of the aneurysm is one of the most significant factors related to risk of rupture, for PComA aneurysms as well as for aneurysms of other locations [272, 125, 188, 192, 267]. There are indications, however, that PComA aneurysms tend to rupture at smaller sizes than other anterior circulation aneurysms [272, 180, 24, 89, 188, 114, 269]. According to an international prospective multicenter study on unruptured intracranial aneurysms (ISUIA) study, the cumulative 5-year rupture risks were 3% <7mm, 15% 7–12mm, 18% 13–24mm and 50% ≥25mm for PComA aneurysms. The risks were 0% <7mm, 3% 7–12mm, 15% 13–24mm and 40% ≥25mm for other aneurysms of anterior circulation [272].

Other relevant factors for the risk of rupture are cardio-vascular risk factors, hemodynamic stress related to angioarchitecture of the vessel tree, and morphology of the aneurysm itself [180, 102, 251, 175, 140, 22]. Given the distinctive natural history of aneurysms at different locations, it seems logical to study morphological characteristics of aneurysms in a location-specific manner to better identify those aneurysms in the risk of rupture, also the small aneurysms that may rupture.

2.3.4.1. Morphological Features

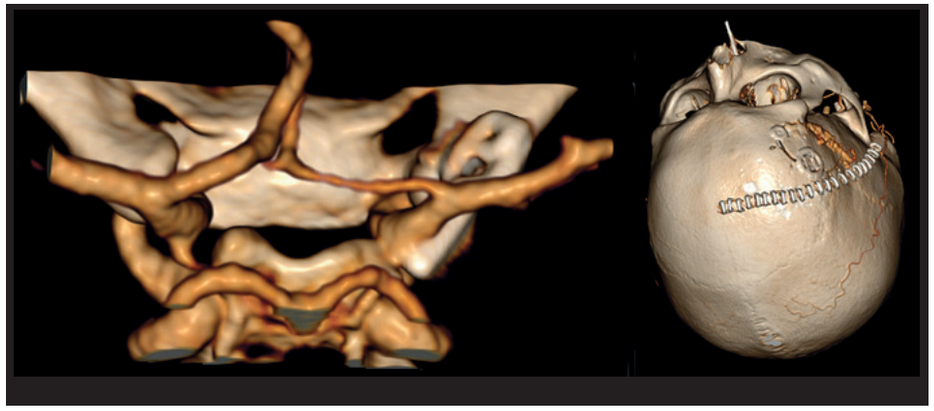
Recently, there have been a few publications on morphology and location-specific risk factors associated with rupture of PComA aneurysms [73, 102,175, 251, 172, 22]. The first larger series of PComA aneurysms was presented by Yasargil in 1984 (n=173) [276]. The other series are from more recent years.

Bleb formation or irregularity of the aneurysm dome (Figure 11), larger aneurysm neck diameter and ICA bifurcation to aneurysm distance have been associated with PComA rupture status [175, 180, 102]. There is variation in morphological factors, which some studies have found to be significant. This might be related to a different study settings or fairly small sample sizes, even after the smallest are left out (n=56–129).

There are few publications stating that the orientation of the PComA aneurysm might be crucial for the risk of rupture. Especially lateral or superolateral projections of the PComA aneurysm dome or larger inflow-angle, describing a more superior dome projection, have been associated with an increased risk of rupture [180, 251, 175, 173].

Figure 11
3-D-CTA-reconstruction of the ruptured PComA aneurysm with a large secondary pouch and irregular dome on the right side.

Figure 13
3D-recunstruction of total aneurysm occlusion after clipping of PComA aneurysm and neat attachment of the bone flap on the skull.



Also, the treatment-related risks might be different for PComA aneurysms of different orientations. A Japanese study reported higher risks of procedure-related complications of surgical clipping, including postoperative cerebral infarction or hematoma formation, for ruptured PComA aneurysms with posterior orientation than those with lateral orientation [73].

Flow Dynamics

The aneurysm formation and rupture is believed to be a multifactorial and a predominantly degenerative process, resulting from a complex interplay of biological processes in the arterial wall and the hemodynamic stimuli on the vessel wall [156]. Cultured vascular endothelial cell studies have shown that disturbed flow conditions and unsteady turbulent stresses damage the endothelium [45, 46].

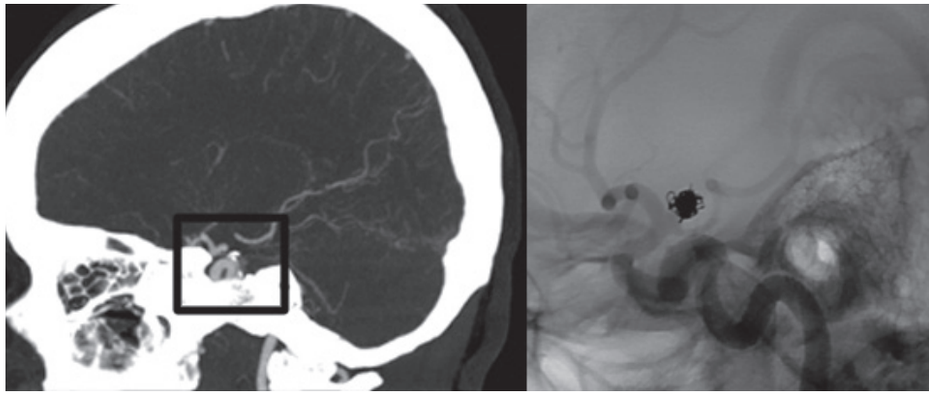
Wall shear stress (WSS), a parameter from computational fluid dynamics analysis, has been investigated in several studies to estimate its relationship with the risk of aneurysm rupture. It seems that lower WSS locally may be associated with an increased risk of aneurysm rupture [282, 176, 175, 31, 274, 26]. Unruptured PComA aneurysms causing oculomotor nerve palsy may have hemodynamic patterns that differ from the patterns of unsymptomatic PComA aneurysms and are closer to those of ruptured aneurysms [176]. There are, however, controversial findings on the WSS, and no highly useful clinical applications as of yet.

Occlusive Treatment of PComA Aneurysms

Microsurgical Clipping

As most posterior communicating artery aneurysms are usually saccular and seldom large, they have been seen as good candidates for clipping of the aneurysm neck [276]. They have been seen as fairly uncomplicated lesions for treatment. The occlusion rate after treatment is usually checked with postoperative CTA angiography and long-term follow-up is seldom routinely needed (Figure 12). The treatment-related risks of unruptured aneurysms seem to be close to 10% for morbidity and 2–3% for mortality [272].

Figure 13
Sagittal CTA image showing the area of interest. On the right, DSA image presenting occlusion of PComA aneurysm by coiling.



According to the Barrow Ruptured Aneurysm Trial, a randomized trial comparing safety and efficacy of microsurgical clipping and endovascular coiling, the patients treated by clipping had significantly higher degree of aneurysm obliteration and a significantly lower rate of recurrence and re-treatment than coiled aneurysms. The outcomes at 6 years showed no differences in the outcome for anterior circulation aneurysms. The outcomes of posterior circulation aneurysms favoured coiling [244]. A Finnish study which also included neuropsychological outcomes has concluded that outcomes seem comparable after early surgical and endovascular treatment of ruptured intracranial aneurysms [139]. One challenge is that these single center studies often reflect the experience and expertise of a high-volume neurosurgical center and the results may not be generalized to all centers world-wide.

Endovascular Coiling

The typical morphology of PComA aneurysms and proximal location along the neurovascular tree also make them optimal for endovascular coil embolization. After some prospective trials on treatment methods of ruptured and unruptured intracranial aneurysms, the endovascular treatment has gained popularity [186, 139, 114, 272, 244, 188]. The International Subarachnoid Hemorrhage Trial assessed the outcome in terms of disability free survival at 1 year after aSAH and treatment to be significantly better after endovascular coiling coiling compared. Because of the selection bias of the study, the results may not be applicable to all patient groups. In the treatment of unruptured aneurysms, the treatment-related risk of morbidity is close to 7%, and mortality 2–3% [272].

The occlusion rate after coiling can be estimated in the DSA angiography after finalizing the procedure (Figure 13). Follow-up angiographies (DSA or MRA) are routinely performed at 6 months, usually at 2 and 5 years, and according to individual needs. There are some indications that coiled PComA aneurysms have a higher recurrence rate than other aneurysms of the anterior

circulation (close to 30%) [170, 38]. The PComA aneurysms lying beside a dominant type posterior communicating artery especially have been significantly associated with recurrence [131]. The rebleedings after treatment are still rare after both endovascular and neurosurgical treatment [186, 187, 244].

Endovascular Advances

To solve the challenges of recurrences and to improve the treatment of wide-necked PComA aneurysms, balloon and stent-assisted coiling techniques have been developed [170, 266]. In light of the current literature, the stent-assisted coiling may be preferred, since it has been associated with better complete occlusion rates of aneurysms at 6 months or later than balloon- assisted coiling. The risks of intraprocedural complications or re-treatment were similar [266].

One Chinese study has compared the complications and outcome after coiling or stent-assisted coiling of PComA aneurysms. The recurrence rates at the latest follow-up (mean 14 months) were significantly lower for stent-assisted coiling group than the simple coiling group (11% and 28% respectively). The procedure-related complication rates were similar (11–12%) [170].

The endovascular technique of flow diversion for the treatment of large, giant or wide-necked aneurysms requires placement of the flow diversion stent or device in the internal carotid artery across the origin of PComA. Small studies have reported PComA arteries demonstrating occlusion or decreased flow if the ostium of PComA has been covered with a flow diversion device. The clinical significance of this finding is not yet clear and the results are controversial [17, 43]. Also, the anterior choroidal artery might be compromised [134], which may lead to ischemia in the optic tract, internal capsule, lateral aspect of thalamus or the midbrain. A recent study found the flow diversion treatment to be ineffective in treating PComA aneurysms associated with fetal PCA, and it should be considered only when conventional treatment options are not feasible [265]. In fact, the indications for flow diversion are still not completely established. Due to the risk of thrombo-embolic complications, dual antiplatelet medication is recommended. Thus, most aneurysms treated by flow diversion are unruptured [211]. However, preliminary results from small series have suggested flow diversion treatment has some value in very small ruptured aneurysms that are untreatable by standard coiling or surgical technique, including blister-like aneurysms [149].

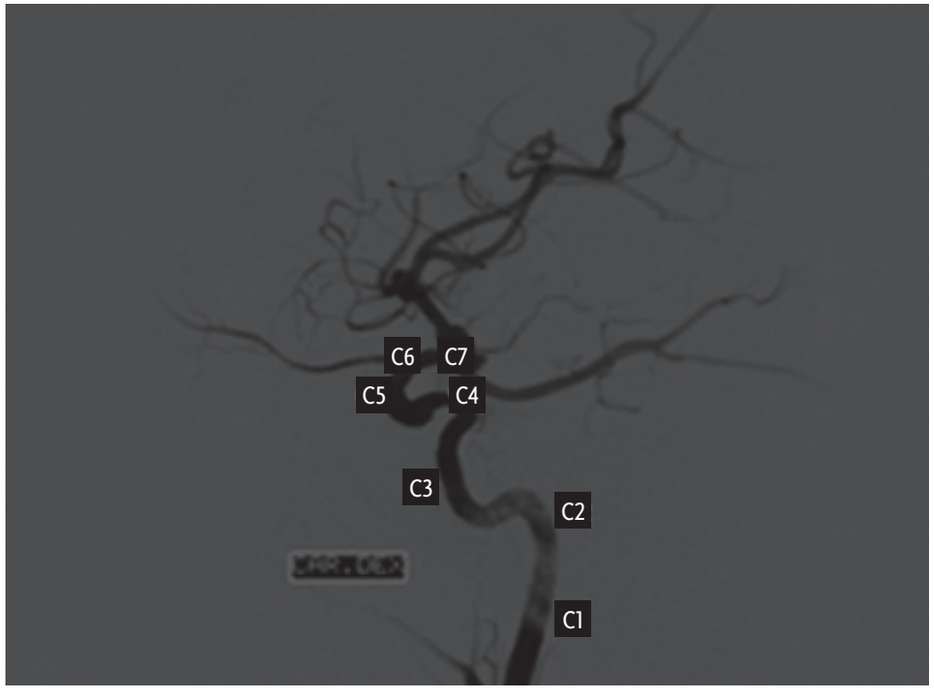
The flow disruption with Woven EndoBridge (WEB) device has also been introduced as an endovascular technique for wide-necked aneurysms after 2010. In WEB treatment, the device is applied into the aneurysm dome at the level of the neck to disrupt the intra-aneurysmal flow and to create intra-aneurysmal thrombosis [210]. The study results so far suggest that the WEB can be an effective method with about 81% occlusion rate with low morbidity (3%) and mortality (2%) [177]. The current indications for WEB are wide-necked aneurysms at bifurcation sites, which makes this technique rarely suitable for PComA aneurysms.

Indirect Surgical Methods

For unclippable aneurysms or difficult intraoperative bleedings, various indirect surgical methods have been used to treat the aneurysm: parent artery sacrification, wrapping with reinforcements, trapping with or without bypass and aneurysmectomy following direct suture of the vessel wall. Among these, wrapping is one way to prevent further bleeding and to save the normal arterial flow [135, 256, 101, 198, 183, 40, 47]. It was used more commonly decades ago, prior to the endovascular era, when the treatment techniques and equipment were limited. Wrapped aneurysms mostly heal or remain stable, but

Figure 14

Presents sagittal carotid DSA showing ICA segments according to classification of Bouthillier: C1 cervical; C2 petrous; C3 lacerum; C4 cavernous; C5 clinoid; C6 ophthalmic and C7 communicating segment.



some may progress or rebleed, which indicates a need for long-term term surveillance after wrapping [135, 47, 256].

A trapping of the internal carotid artery with or without extracranial-intracranial bypass has been used to treat rarely seen large or giant PComA aneurysms, blood blister-like aneurysms, and ICA rupture during the aneurysm surgery. At times, it has been used for PComA aneurysms with a challenging morphology, where clipping of the aneurysm neck seems impossible. As this technique requires occlusion of the internal carotid artery, it puts the distal parts of the vessel tree beyond the trapping site at risk of decreased blood flow, which potentially causes brain tissue ischemia. This is why trapping is nowadays seldom used as a first line treatment method. It also requires meticulous preoperative planning in order to evaluate if revascularization procedures will be needed to decrease the risk of brain infarction [33, 126, 158].

2.5. Microsurgical Anatomy of the Internal Carotid Artery (ICA) and the PComA

2.5.1. Segments of the ICA

Fischer´s classification on segments of the ICA, published in 1938, was based on angiographic course of the intracranial ICA rather than branches or anatomic compartment. The segments were numbers opposite to the direction of blood flow. In the 1980s, Rhoton

used a classification where the ICA was divided into four segments: C1 cervical; C2 petrous; C3 cavernous and C4 supraclinoid portion [79]. Bouthillier et al. published a new classification in 1996 [15]. Bouthillier´s classification includes the entire ICA, describing the segments according to the surrounding anatomical compartments and numbering the segments in the direction of blood flow (Figure 14).

2.5.2. Communicating Segment

Posterior communicating artery aneurysms lie in the communicating segment of the ICA, which extend from just below the origin of the posterior communicating artery to the bifurcation of the ICA [15]. The posterior communicating artery usually originates from the inferolateral wall of the ICA within the carotid cistern. There are about 2–10 small perforating branches originating from the PComA, called the anterior thalamoperforating arteries [275].

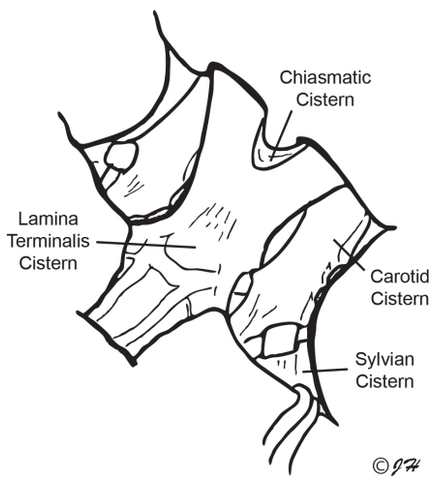
The anterior choroidal artery (AChA) arises 2–5mm distal to the posterior communicating artery, and it also has the origin in the inferolateral aspect of the ICA. The AChA may arise as a single trunk, or as 2-4 independent vessels. The perforant arteries of the ICA around the AChA pass upwards and enter the anterior perforated substance. The uncal branches of the AChA may appear as medial striate arteries coursing beneath the bifurcation [79, 275, 276].

Subarachnoid Cisterns

Understanding relationship of the subarachnoid cisterns to the aneurysm is important in order to be able to perform an accurate dissection during a microsurgical procedure. The posterior communicating artery originates in the carotid cistern [276] (Figure 15). It carries its own sleeve of arachnoid to the interpeduncular cistern where it encounters the posterior cerebral artery (PCA).

There are some points of arachnoid thickening and fixation: i) the corner joining the uncus, tentorium and the oculomotor nerve; ii) the exit of the oculomotor nerve into the cavernous sinus and iii) the attachment of arachnoid sleeves of PComA and oculomotor nerve over the Liliequist´s membrane. At times, there are dense adherences between the PComA and the posterior clinoid process. The PComA aneurysm may be covered by the arachnoid of the carotid cistern, and as it enlarges it might come in contact with the arachnoid of the crural and interpeduncular cisterns, with potential attachments [276]. An initial intracranial step during microsurgical procedures is the opening of the chiasmatic and carotid cisterns to release cerebrospinal fluid (CSF). This enables the brain to relax and the working space to expand without retraction [157, 161].

Figure 15
Schematic drawing of the frontobasal subarachnoid cisterns.



Clinoid Processes

The anterior and posterior clinoid processes are bony, prominent landmarks at the skull base anterior and posterior to the ICA and PComA origin (Figure 16). If the PComA origin and aneurysm are located proximally or the anterior process is large, this bony process may cover the aneurysm neck during the microsurgical procedure. Drilling and removing this bony structure, e.g. anterior clinoidectomy, may be needed [276, 79, 157, 161].

As the posterior communicating artery courses towards the interpeduncular cistern, it runs over the posterior clinoid process and may be attached to it if the process is prominent. At times, an actual groove has been detected in the posterior clinoid process, where the PComA crosses it. This kind of adherence may decrease the mobility of the PComA during a procedure [276, 79].

Oculomotor Nerve

The PComA aneurysms are situated between critical anatomical structures: the optic nerve on the medial side and the oculomotor nerve on the lateral aspect (Figure 17). The oculomotor nerve or the third nerve originates from the interpeduncular fossa of the midbrain, courses between the posterior cerebral artery (PCA) and the superior cerebellar artery (SCA), attaches to the membrane of Liliequist, and rises to the oculomotor triangle to exit the subarachnoid space and travel in the roof of cavernous sinus below the anterior clinoid process [157].

The PComA aneurysms often project towards the oculomotor nerve, and there may be dense adherences between the nerve and the aneurysm. This also explains why oculomotor nerve palsy may be the presenting symptom of PComA aneurysm even prior to aneurysm rupture. The manipulation of the oculomotor nerve should be carefully avoided as this easily causes dysfunction. Also, electro-coagulation close to the optic and oculomotor nerves should be avoided; the nerve structures may be injured by the heat even without physical manipulation [276, 79, 157, 194].

Tentorium and Temporal Lobe

The anterior edge of tentorium attaches to the anterior clinoid process and the medial edge of the middle cranial fossa at the skull base. The tentorial edge may be close to the

Figure 16
3D-CTA reconstruction of the PComA aneurysms with prominent, bony anterior clinoid processes.

ICA and the PComA aneurysm, which may limit the working space during the procedure. The dome of the aneurysm may be attached to the edge of the tentorium or it may extend above or below it [79,194, 276]. A PComA aneurysm can be projected towards the uncus of the temporal lobe, and in some cases, it may be attached or even have pushed itself into the parenchyma of the brain [276].

Posterior Communicating Artery

The posterior communicating artery origin can usually be found at inferolateral or posterior wall of the ICA. Sometimes, the PComA aneurysm may overlie on top of the origin, obscuring the view during a procedure [276]. The diameter of the PComA often varies (0.4–4mm, average 1.4mm). In most cases, it is half or less than a half of the caliber of the posterior cerebral artery (PCA). In about one tenth of the cases, the PComA is of similar caliber to the PCA and in about one fourth it is larger than PCA. When the PComA is larger than P1 segment of the PCA, and the PCA is hypoplastic or absent, the variant is called fetal PCA. In these cases, the vascular supply of the PCA area comes from the anterior circulation [276].

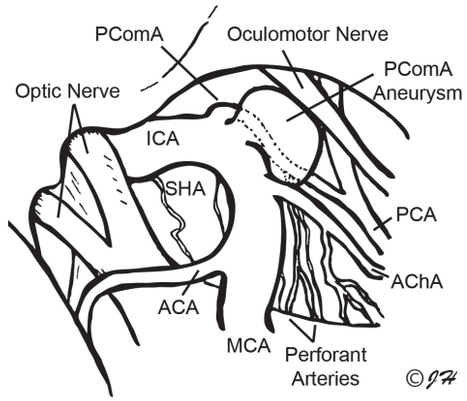
Hypoplasia or aplasia of the PComA is also common (3–11%), and there are other rare anatomical variations: PComA fenestration and PComA duplication [79, 275, 276].

Thalamoperforating Arteries

The thalamoperforating arteries, small perforant branches arising from the posterior communicating artery, supply the inferior optic chiasm, optic tract, mammillary bodies, hypothalamus and parts of thalamus [275, 276] (Figure 18). Most of these small branches vary in size. One branch is usually a larger vessel that passes regularly in front of the mammillary bodies entering the parenchyma in the wall of the 3rd ventricle. It is called the premammillary artery.

Figure 17

Schematic drawing of the anatomical relationships of the PComA aneurysm and the oculomotor nerve and other vascular and neural structures close by. A superolateral view.



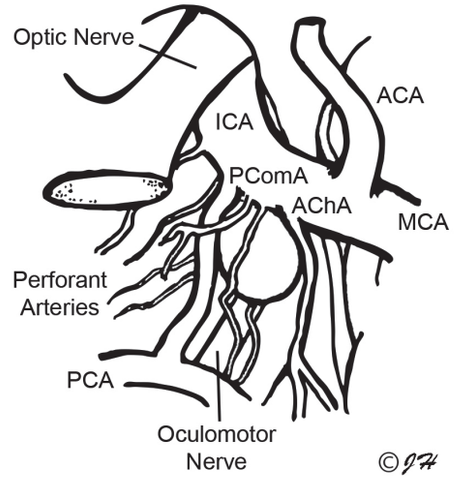
ICA: Internal carotid artery, PComA: Posterior communicating artery, PCA: Posterior Cerebral artery, ACA: Anterior cerebral artery, MCA: Medial cerebral artery, AChA: Anterior choroidal artery, SHA: Superior hypophyseal artery

Anterior Choroidal Artery

The origin and diameter of the anterior choroidal artery (AChA) are more constant (diameter 0.5–2.1mm, average 1.0mm). From its origin distal to the PComA, the AChA courses posteriorly above the PComA, passes through the choroid fissure and joins the choroid plexus in the temporal horn and atrium. The small but important branches from AChA supply the optic radiations, the basal ganglia including the tail of the caudate nucleus, midbrain, thalamus and parts of the internal capsule [79]. With larger PComA aneurysms, the AChA may be covered by and adherent to the dome of the aneurysm. It should be identified and spared during an occlusive treatment of the PComA aneurysm [276].

Figure 18

Perforant arteries include thalamoperforating arteries arising from the PComA and perforant arteries from the posterior surface of the ICA. A schematic drawing, view from up towards the base of the skull.



ICA: Internal carotid artery, PComA: Posterior communicating artery, PCA: Posterior Cerebral artery, ACA: Anterior cerebral artery, MCA: Medial cerebral artery, AChA: Anterior choroidal artery

Microsurgical Technique

Approach

The most widely used openings for PComA aneurysms are pterional and lateral supraorbital (LSO) approach. When preparing for these approaches, the patient is positioned supine, head and shoulders elevated (Figure 19). The head is rotated 15 to 20 degrees away from the side of the aneurysm. The head is extended about 20 degrees, allowing gravitation to retract the frontal lobe away from the base of the skull. This head positioning aligns the sylvian fissure vertically, letting the frontal and temporal lobes to fall aside naturally.

In the pterional approach, a semicircular skin incision extends from the zygomatic arch anterior to tragus to the midline, just behind the hairline. The temporalis muscle is split along the direction of the muscle fibres and retracted frontobasally with the scalp flap [157, 161]. The superior orbital rim and the anterior zygomatic arch are exposed. The dura is carefully detached using a single temporal burr hole allowing a frontotemporal craniotomy. The pterion and the lesser wing of the sphenoid medially to the superior orbital fissure, as well as the anterior clinoid process, may be drilled to flatten the space between the anterior and the medial cranial fossa to improve the visualization and the working space [157, 161].

The LSO approach is a more subfrontal and smaller modification of the pterional approach with a similar head positioning (Figure 20). The exact positioning depends on the pathology, its orientation and meticu-

Figure 19

Patient with ruptured PComA aneurysm has been prepared for the LSO approach and microsurgical treatment of the aneurysm. Head is fixed to a Sugita frame.

Figure 20
Opening of the skin and temporal muscle prior to the craniotomy during the LSO approach on the left side of the skull.

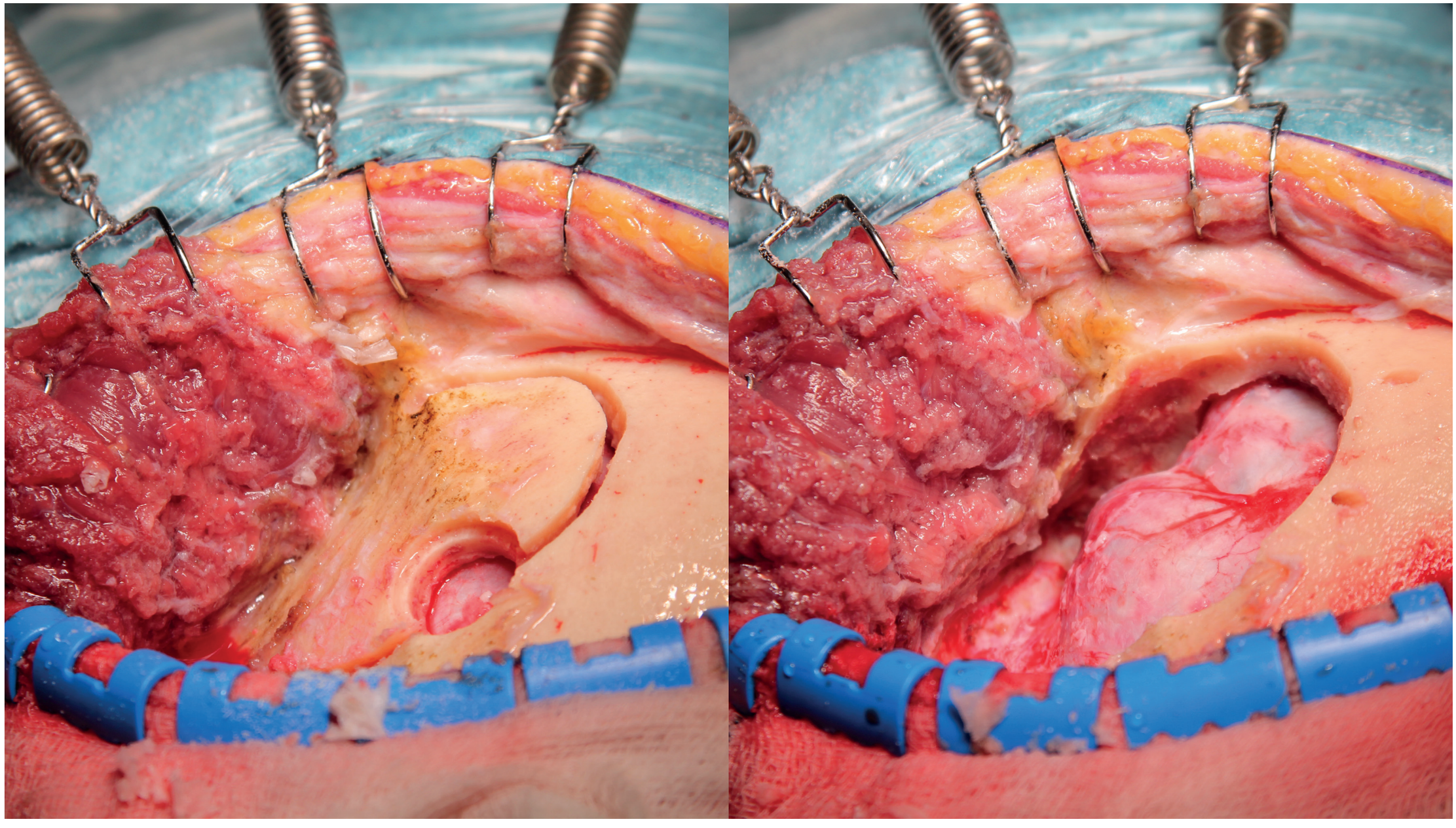
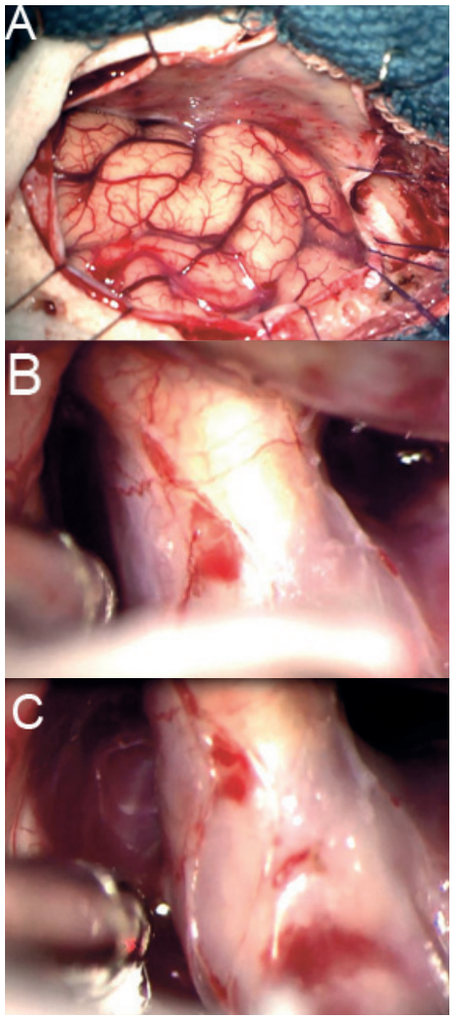


Figure 21
View from the operating microscope prior and during intradural dissection: A) LSO approach on the right, dural opening with lift-up sutures, B) frontobasal view with right optic nerve, right internal carotid artery and the neck of the PComA aneurysm after opening of the carotid cistern, C) PComA and a perforant artery posteromedially to the ICA.



lous preoperative planning. The curved skin incision is positioned just behind the hairline. The skin-muscle flap is opened as a one-layer block and only the anterior part of the temporal muscle is split off and retracted frontally to expose the superior orbital rim and the anterior zygomatic arch. A single burr hole at the superior insertion of the temporal muscle is used to detach the dura and a small keyhole craniotomy limited to the Sylvian fissure laterally. To finalize the opening, the lateral sphenoid ridge is drilled down to minimize the need for retraction, and the dura is opened in curved fashion, base down, and elevated with lift-up sutures [161].

Intradural Dissection

The intradural dissection starts with identifying the optic nerve and the ICA with opening of the basal cisterns to release cerebrospinal fluid (CSF) to aid the brain to relax and to increase the working space [161]. Especially low-lying PComA aneurysms can usually be occluded after this without opening the Sylvian Fissure (Figure 21). Opening the proximal fissure may improve the visualization of the ICA´s communicating segment and the ICA bifurcation, if needed. The frontal lobe retraction on the medial orbital gyrus can be used at times to improve the view without causing retraction to the PComA aneurysm. Opening of the lamina terminalis cistern is at times appropriate.

Proximal Control and Dissection

Dissection of the ICA proximally to the apex of optic-carotid triangle allows control proximal to the PComA aneurysm. At times, anterior clinoidectomy may be needed for sufficient proximal control, and usually a limited removal of the tip and body of the anterior clinoid process is enough. The relation between aneurysm neck and the PComA and its branches as well as the AChA must be identified with caution.

The adhesions to the tentorium, posterior clinoid process or AChA may be released to allow safe dome dissection and clip placement. The manipulation of the oculomotor nerve should be avoided. The arachnoid adhesions between the PComA aneurysm and the oculomotor nerve are difficult to separate without causing an oculomotor nerve palsy (ONP). This is why it is better to occlude the neck of the aneurysm first and then to cut through the aneurysm rather than try to separate it from the oculomotor nerve [276, 79, 194, 157].

Aneurysm Clipping and Closure

After dissection of the aneurysm and its neck, the PComA aneurysm can often be occluded with a single clip. Temporary clip in the proximal ICA and even to the PComA may be used, if needed, to soften the aneurysm dome and to control the carotid flow and bleeding in case of a fragile dome (Figure 22). Attention should be paid to place the clip over the shoulder of the PComA origin, between the PComA origin and the dome, so that the origin is not left on the same side with the dome, allowing retrograde filling. After optimal look-

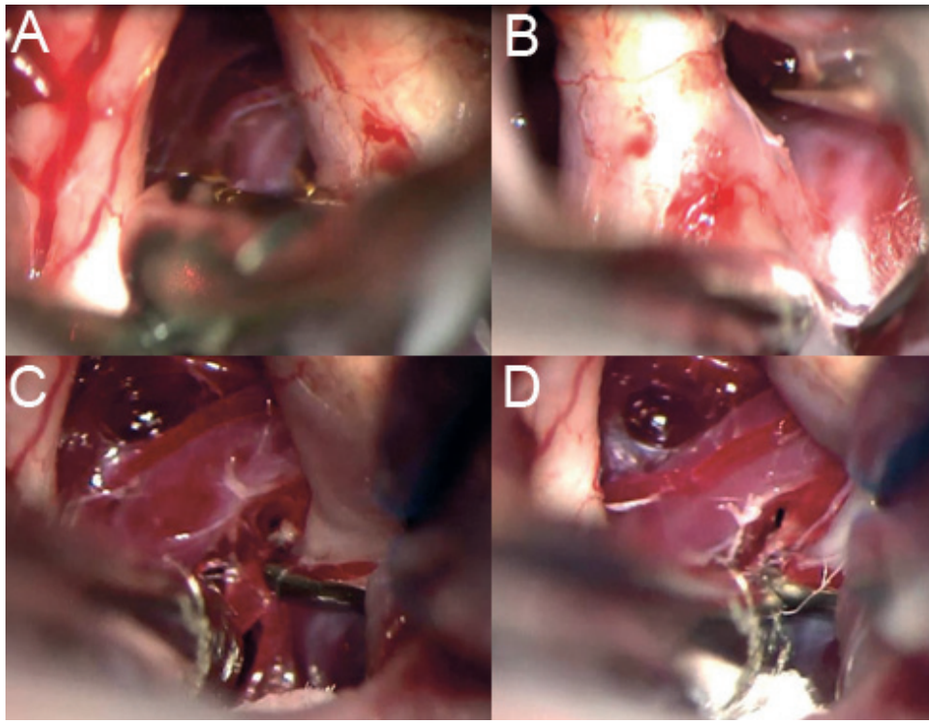


Figure 22
A) Placing a temporary clip to the PComA, B) placing a straight titanium clip to the neck of the PComA aneurysm, C) a performant artery caught by the aneurysm clip D) PComA and performant arteries are open after replacing the aneurysm clip.

ing clip placement, the aneurysm may be punctured to decompress the oculomotor nerve and to open the view behind the aneurysm. Clip tips may sometimes catch the PComA or its perforators or the AChA, as they course behind the aneurysm and the ICA. The clip may still be re-positioned if needed with the aid of the temporal clip occluding the ICA. Clipping some larger aneurysms or those with intraluminal calcification or thrombus may benefit from tandem clipping or multiple clips [157, 161]. Indocyanine green video angiography (ICG angiography) is often used to make sure the PComA aneurysm is not filling and the arterial branches are open [44, 92, 224] (Figure 23). Intraoperative micro-Doppler ultrasonography is also a useful tool for evaluating arterial flow and verifying proper clip placement [107 241]. In complex cases, even intraoperative DSA may be needed [253]. The final step of the procedure is assuring meticulous hemostasis and closure layer by layer.

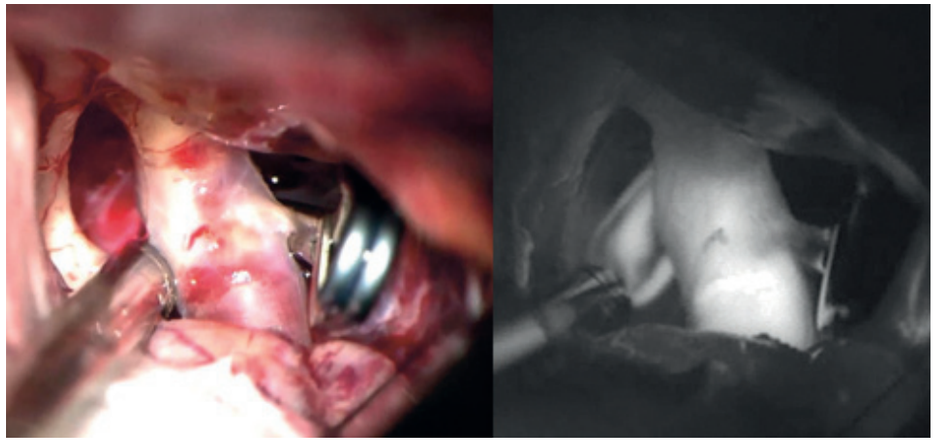


Figure 23
Indocyanine green (ICG) angiography shows the intra-arterial flow in the right ICA, the PComA and a small carotid perforant artery after successful clipping of the PComA aneurysm.

Outcome after PComA Aneurysm Rupture

Earlier Patient Series on PComA Aneurysms

There are few earlier clinical series on treatment of patients with PComA aneurysms [255, 73, 232, 276]. Even today, the largest and most detailed series is from 1984 by Yasargil, who reported the surgical anatomy and treatment of 173 patients with PComA aneurysms [276]. In this series, 95% of good grade patients made good recovery, compared to 60% of the grade III patients and 20% of the grade IV patients. The proportion of poor grade patients was low (7%).

Previous studies report a moderate number of lacunar infarctions (5%) and severe bleeding or spasm-related neurological complications (7%) as risks of treatment for ruptured or unruptured PComA aneurysms [255, 73, 232, 276]. The PComA patients who suffered from aSAH had a higher risk of postoperative infarction [255]. In the Yasargil series, one patient had a MCA injury and an adjacent infarction, and another one got a tear on the aneurysm neck during the clip application and the ICA had to be closed above and below the lesion (trapped) followed by severe morbidity [276].

The preoperative clinical condition of the treated patients seemed to be the most important factor in determining the postoperative morbidity and mortality, according to Yasargil [276]. There was no statistical analysis performed to support this statement, but the preoperative and postoperative clinical states and their relation seemed to support the finding.

Oculomotor Nerve Palsy

A large number of publications have focused on an oculomotor nerve palsy, a specific problem related to PcomA aneurysms, which may affect up to every third PcomA aneurysm patient [242, 132, 27, 129, 87, 19, 281, 61, 163, 119]. The potential mechanisms of ONP secondary to PcomA aneurysms include i) a direct compression of the nerve by the aneurysm dome, ii) the irritation of the nerve by the subarachnoid hemorrhage iii) the pulsating effect caused by the aneurysm or iv) a combination of these [242, 281].

Several publications have studied the efficacy of surgical clipping and endovascular coiling in treatment and recovery of ONP [132, 27, 129, 87, 19, 281, 61, 163, 119]. The studies have been limited by their relative small sample sizes. A complete ONP recovery has been detected for about 55–85% of clipped and 32–71% of coiled PcomA aneurysm patients [16, 19, 27, 87]. A meta-analysis pooling together the data from previous studies found a superiority of clipping over coiling for the complete recovery of the ONP after aSAH. No significant differences considering the outcome could be observed between clipping and coiling in treatment of unruptured PcomA aneurysms with ONP [281].

Aims of the study

1. To study the vascular anatomy of the internal carotid artery and the posterior communicating artery using computed tomography angiography images. To assess typical morphological features and anatomical variants related to posterior communicating artery aneurysms and specifically to aneurysm rupture.

2. To determine the treatment and outcome of subarachnoid hemorrhage patients with ruptured PcomA aneurysm. Are there specific challenges regarding the treatment of aneurysms in this location? What are the risk factors for an impaired outcome? Are there ways to improve the outcome?

3. To examine if there is long-term excess mortality after aneurysmal subarachnoid hemorrhage. What are the causes of death of these patients? Are there risk factors for long-term excess mortality? Some of these factors could be targeted and the excess mortality reduced.

Patients, materials and methods

These studies are based on Helsinki Cerebral Aneurysm Research Database, and specifically retrospective data collected on 7289 aneurysm patients treated between 1980 and 2014 in the Helsinki University Hospital, Finland. This hospital is responsible for the treatment of all neurosurgical and neurovascular patients in the Southern Finland, with a catchment area of 1.8 million people. Each publication (I – III) includes a subgroup of these 7 289 patients with intracranial aneurysms; 5 586 of them (77%) were treated for aneurysmal subarachnoid hemorrhage.

All the publications are epidemiological studies. The publications I – II are descriptive studies or consecutive, large clinical series. The third publication is a cohort study. All the studies have been carried out in co-operation with a data scientist, and the statistical analyses have been carried out using the R environment for statistical computing [184] and the SPSS software [111]. In general, P values <0.05 have been the criteria for statistical significance using 95% confidence intervals (CIs).

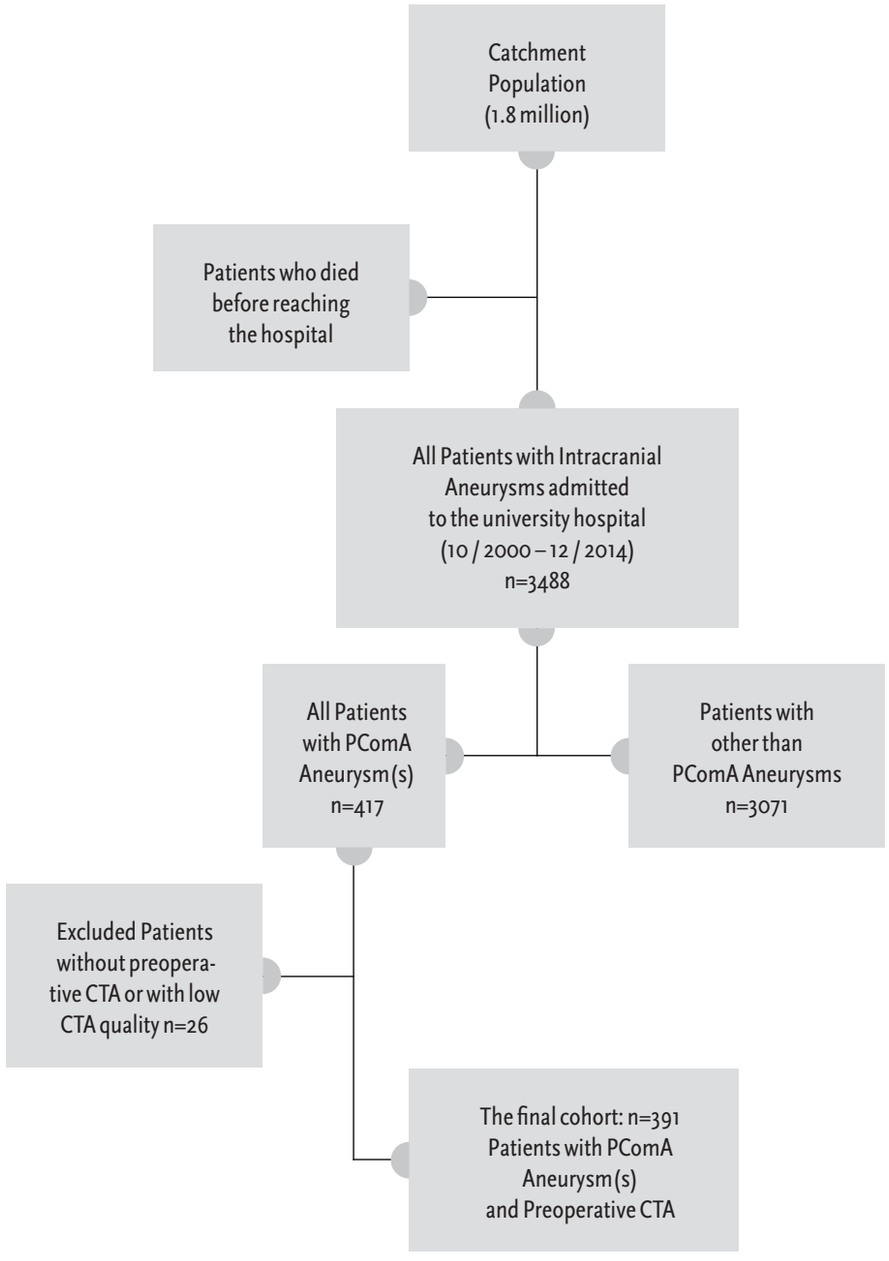
Publication I:
CTA Analysis and Assessment of Morphological Factors Related to Rupture in 413 Posterior Communicating Artery Aneurysms

4.1.1. Patients

Publication I consists of patients who were treated for a PcomA aneurysm between November 2000 and December 2014 at Helsinki University Hospital. There were a total of 3488 intracranial aneurysm patients admitted to the Helsinki University Hospital during this time period. Of these patients, 417 (12%) had PcomA aneurysm(s). The diagnosis of PcomA aneurysm was based on CTA, MRA or DSA. Only patients with pre-treatment CTA were included in this study. Patients with only MRA (n=6) or DSA images (n=10) or with missing preoperative image data (n=5) were excluded. Five patients were excluded because of low preoperative CTA image quality. The study group consisted of 391 patients with either ruptured (n=258) or unruptured (n=155) PcomA aneurysm(s).

The clinical and radiological data on all the 391 PcomA aneurysm patients were reviewed for relevant clinical and radiological information, focusing on the morphology and CT angiography analysis. The study group included patients who were treated actively (microneurosurgically n=315, 76% or endovascularily n=42, 10%) and patients who were followed up (n=54, 13%).

Figure 24
Flow Chart of the selection process of the study patients for Publication I.



Radiological Data

The admission CT and CTA images were evaluated with the Impax Client application using maximum intensity projection (MIP) reconstructions. CTAs were obtained with a 32-row helical CT scanner (GE LightSpeed VCT) after administration of a 70-cm^3 intravenous contrast agent (5ml/s). After the bolus had reached the internal carotid artery at the level of C3-4, the imaging was initiated (slice thickness 0.625mm, pitch 0.984:1, 120kV, 100-500mA; field of view 23cm, rotation speed 0.4 s). Prior to 2007, we used a multislice helical CT scanner with 4-16 detector rows (GE Lightspeed QX) with fixed timing in contrast administration (18s prior image acquisitions for patients under 60 years old, 20s for patients over 60 years old) and 1.25mm slice thickness. The imaged region started from the level of the first cervical vertebra and continued above the top of the skull.

Measurements included the total number of aneurysms, aneurysm rupture status, PcomA aneurysm size (length, width, neck) and regularity of the dome (visually assessed, by a radiologist and a neurosurgeon). The size of the aneurysm was defined as the maximum diameter of the aneurysm. Aspect ratios (length divided by the neck) and bottleneck factors (width divided by the neck) of the ruptured and unruptured aneurysms were calculated. Aneurysm orientation and its relation to the tentorium, mesial temporal lobe and clinoid processes were determined. If the aneurysm orientation was in between the two different orientations, the closest one was chosen.

Anatomical measurements were also taken of the intracranial internal carotid artery (length, diameter and angle of the supraclinoid ICA using the coronal plane) and posterior communicating artery (level of the origin from the sagittal plane, diameter, type of origin and existence of anatomical variations using the axial plane). Three-dimensional images were used to evaluate the origin of the PcomA if the two-dimensional images were not clearly interpretable.

Statistical Analysis

Continuous variables were compared using Student's t test and categorical variables using the chi-squared test. Collinearity of the variables was evaluated using variate inflation factor (VIF). The VIFs of all the chosen parameters were <2.0, meaning they could be included in the multivariable analysis. The parameters found to be statistically significant in univariable analysis were further analyzed using multivariable logistic regression (backward elimination) to identify those that remained significant when accounting for all relevant parameters.

Publication II:
Occlusive Treatment of Ruptured Posterior Communicating Artery Aneurysms Riskier than Expected – Treatment and Outcome of 620 Consecutive Patients

Patients

Publication II includes all the aSAH patients who have been treated because of a ruptured PcomA aneurysm (n=620) in the Department of Neurosurgery in Helsinki University Hospital between 1980 and 2014. Seven patients were excluded because they were primarily treated at other hospitals.

All of the study patients suffered from aneurysmal subarachnoid hemorrhage caused by a ruptured PcomA aneurysm. All but one had saccular aneurysms, and 33% of patients (n=202) had multiple aneurysms. The majority of the patients (n=583, 94%) were treated actively, meaning they received treatment aiming at the occlusion of the PcomA aneurysm.

Clinical and Radiological Data and Follow-Up

The PcomA aneurysm patients´ clinical and radiological data were reviewed for relevant information concerning the admission to hospital, the primary treatment period and

treatment method as well as the follow-up. The severity of bleeding was graded according to Fisher grade (Fisher I–IV) [68], preoperative clinical condition using Hunt&Hess grade (HH1–5) [108] and clinical outcome using modified Rankin Scale (mRS0–6) [219]. Good outcome was defined as mRS0-2, unfavorable outcome as mRS>2. For all patients who had no contraindications, a post-operative angiography (DSA, or CTA) was conducted the same or the next day following the procedure. The patients who got endovascular treatment had a routine DSA imagining at 6 months. Other imaging controls were conducted on the basis of individual needs. An experienced radiologist and a neurosurgeon collected the data and reviewed all the images.

IVH was defined as any blood in the ventricular system (excluding thin layers of blood in the occipital horns several days after the ictus) and SDH as any blood in the subdural space. ICH referred to any intracerebral hematoma with a minimum diameter of 10mm. Also, the radiological features of the ruptured PComA aneurysm were evaluated. Any irregularity of the aneurysm dome was visually assessed. Preoperative hydrocephalus referred to dilated ventricles and symptoms like decreased level of consciousness causing the need for extraventricular drain (EVD).

There were altogether 23 neurosurgeons or neurointerventionalists performing the occlusive treatment for the ruptured PComA aneurysms during the follow-up period. The treatment methods included microsurgical clipping, endovascular coiling, a combination of these two techniques or indirect means like carotid ligation or trapping.

The occlusion rate of the treated aneurysm, as well as clinical and radiological complications were reported. Probable causes of the ischemic complications were classified. Diagnosis of the delayed cerebral vasospasm was based on clinical and radiological findings. Clinically, it was classified as severe, if both deterioration of consciousness and focal deficits were the symptoms. Patients requiring a shunt suffered from symptomatic hydrocephalus postoperatively (EVD or no EVD previously).

All patients had a post-operative clinical checkup at three to six months after the aSAH, and many were followed up until one year after the treatment. If the patient had favorable recovery at the early checkup, the one-year check-up was not routinely organized. There were 22 patients who were lost to follow-up after discharge but had not died during the first year after aSAH. All the deaths were verified from Population Register Center, and the death certificates were acquired from Statistics Finland.

Statistical Methods

Different categorical variables possibly related to the outcome and their statistical significance were evaluated using Pearson´s Chi-squared test. Multivariable analyses with logistic regression were calculated to estimate independent risk factors for impaired outcome after the rupture of PcomA aneurysm. In addition, likelihood ratio tests were used for variables with multiple levels or categories.

We chose patient-related preoperative and postoperative parameters potentially related to outcome and evaluated their effect on clinical outcome at one-year follow-up. Since some of the parameters are related to each other (e.g. severity of bleeding and clinical condition, or artery occlusions and occlusive treatment-related ischemias), we calculated the collinearity of the variables using variance inflation factor (VIF), and made sure that their correlation was not too high (>10) to distract the results. The VIF of all the chosen parameters were <2.5, meaning they could be included in the multivariable analysis.

Publication III:
Long-Term Excess Mortality after Aneurysmal Subarachnoid Hemorrhage

Patients

Publication III is based on data of 4228 aSAH patients treated between 1980 and 2007 in Helsinki University Hospital. Patients with conditions other than saccular aneurysms, foreign patients and patients treated primarily at other neurosurgical centers were excluded (n=270). There were nine patients who were lost during follow-up within the first year after aSAH. Of the remaining 3 949 saccular aneurysm patients, those who survived a minimum of one year after the initial aSAH, were included. The final study cohort consists of 3078 aSAH one-year-survivors.

Clinical Data

The clinical and radiological data of these patients were recorded in the Helsinki Cerebral Aneurysm Research database and reviewed for this study. The follow-up started one year after the initial aSAH event and continued until death or until the end of the year 2012. There was a theoretical minimum follow-up of at least five years for each patient.

The diagnosis of SAH was based on computed tomography (CT) and/or lumbar puncture. A ruptured aneurysm was identified by using DSA, CTA or MRA. The time of death or vital status at the end of the year 2012 were obtained from the Population Register Center, which contains the information on all residents in Finland. The death certificates of the deceased patients were collected from Statistics Finland.

The initial clinical condition of patients upon admission was evaluated using the Hunt & Hess grading scale [108]. Patients were grouped into active or conservative treatment groups for data analyses. The treatment was considered conservative when the patient did not receive any kind of neurosurgical or endovascular intervention aimed at the occlusion of the ruptured aneurysm at any point during the whole follow-up period.

Follow-Up

The clinical condition at three and 12 months after the aSAH event was evaluated using the Glasgow outcome score (GOS5-1) [120]. After favorable initial outcome at three months, another evaluation at 12 months was not routinely organized. The information on clinical condition was carried forward from the clinical control closest to the one-year mark for those patients for whom the one year clinical follow-up data were missing. The total follow-up time was 48 918 patient-years with a median follow-up of 15 years per patient (range 1–33 years).

Statistical Methods

Excess mortality describes the excess risk of death that a patient has compared to the risk of death of people with similar demographic characteristics in the same population. To measure excess mortality in this study, a relative survival ratio (RSR) was calculated by dividing the observed survival time of treated aSAH patients by the expected survival time. The expected survival was derived by using the Ederer II method [58], [90] for the mortality rates of the Finnish population that had been matched for age, sex and calendar time. These data were obtained from Statistics Finland. The 95% CIs for RSRs were constructed on the log cumulative hazard scale, and the variance of the observed survival proportion was estimated using Greenwood's method [58]. ❦

Results

Posterior Communicating Artery Aneurysms

Incidence of PcomA Aneurysms

There were altogether 7 289 patients treated for intracranial aneurysms in Helsinki University Hospital between 1980 and 2014. Most of them were treated because of aneurysm rupture and aSAH (n=5 586). Of these aSAH patients, 627 were treated for ruptured PcomA aneurysms, meaning 11% of the ruptured aneurysms were PcomA aneurysms (Huhtakangas et al, unpublished results).

Morphological Characteristics of PcomA Aneurysms and Parent Vessels (Publication I)

In Publication I, we studied the morphology of 413 PcomA aneurysms. Of these aneurysms, 258 (62%) were ruptured and 155 (38%) unruptured. The PcomA aneurysms represented consecutive cases, treated microsurgically (n=315, 76%), endovascularily (n=42, 10%) or conservatively meaning that they were followed-up (n=54, 13%).

In CTAs, the most marked morphological features of the PcomA aneurysms were: (1) saccular dome (99%), (2) inferoposterior dome orientation (42%), (3) infrequency of large or giant aneurysms (4%), (4) narrow neck compared to the aneurysm size (74% aspect ratio ≥ 1.5), (5) PcomA originating directly from the aneurysm neck or dome (28%), and (6) a fetal or dominant PcomA on the side of the aneurysm (35%). The morphological characteristics of ruptured and unruptured PcomA aneurysms and results after the multivariable analysis are presented in Table 5.

Table 5
Morphological Characteristics and Univariable Analysis of 413 PcomA Aneurysms

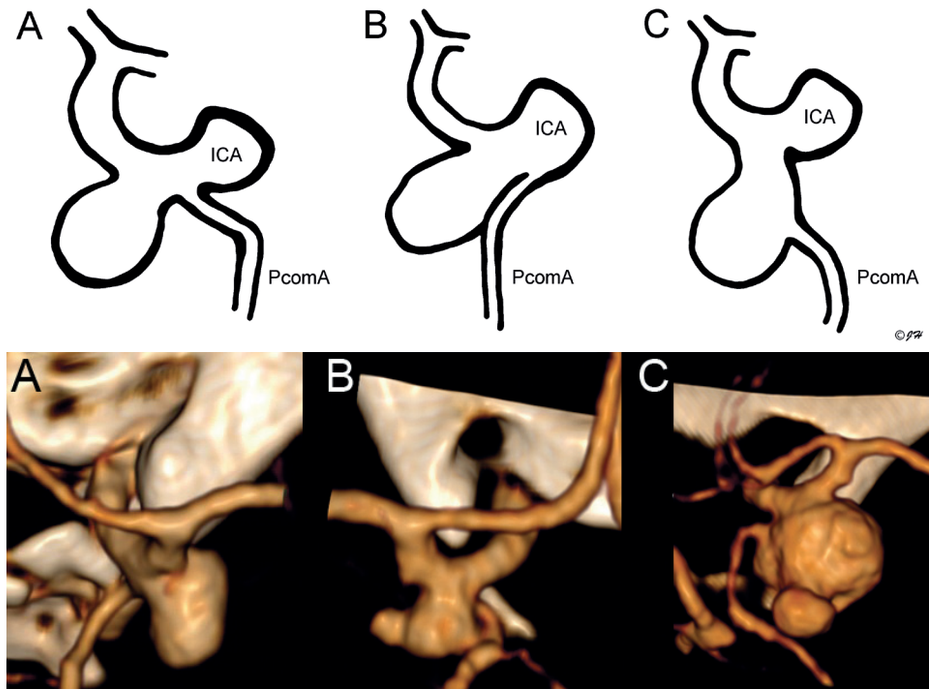
Morphological Parameters	Ruptured PcomA Aneurysms n=258	Unruptured PcomA Aneurysms n=155	Statistically Significant Difference p Value
Size, mm	7.9 (±3.4)	5.2 (±3.5)	<0.001
Length, mm	7.7 (±3.2)	4.9 (±3.5)	<0.001
Width, mm	5.7 (±3.1)	4.1 (±2.8)	<0.001
Neck, mm	3.7 (±1.6)	3.1 (±1.3)	<0.001
Aspect Ratio (length/neck)	2.2 (±0.9)	1.6 (±0.9)	<0.001
Bottle Neck Factor (width/neck)	1.6 (±0.7)	1.3 (±0.6)	<0.001
Irregular Surface (n)	230 (89%)	52 (34%)	<0.001
Length of Intracranial ICA, mm	10.0 (±2.5)	10.2 (±2.6)	0.393
Diameter of ICA, mm (at the level of skull base)	3.0 (±0.6)	3.2 (±0.7)	0.004
PcomA Origin, Distance from the Skull Base, mm	3.3 (±1.9)	3.6 (±2.2)	0.147
Diameter of PcomA, mm	1.3 (±0.6)	1.2 (±0.6)	0.091
Fetal PCA (n)	70 (27%)	27 (17%)	0.069
Relation to Tentorium Supratentorial At the level of Tentorium Infratentorial	 173 (67%) 81 (31%) 4 (2%)	 114 (74%) 33 (21%) 8 (5%)	 0.014
Total	**258 (100%)**	**12**	**155 (100%)**

Parameters are presented as mean values (with standard deviation, SD), or number of aneurysms (% within the group).

Size
Most of the ruptured PcomA aneurysms were medium sized, 7–14 mm (n=146, 57%), whereas most unruptured aneurysms were smaller than 7 mm (n=119, 77%). Large or giant PcomA aneurysms were few (n=18, 4%). Apart from only one ruptured giant PcomA aneurysm, there were ruptured and unruptured PcomA aneurysms in every other size groups. In general, the ruptured PcomA aneurysms were larger (mean size 8.0 vs. 5.2mm), longer (mean length 7.7 vs. 4.9mm) and wider (mean width 5.7 vs. 4.1mm) than the unruptured aneurysms ($p< 0.05$ for all, 95% CI). Among the ruptured PcomA aneurysms, 38% (n=99) were smaller than 7 mm.

Dome Orientation
Inferoposterior, posterior and inferolateral orientations were the most common alignments among the PcomA aneurysms (42%, 20% and 17%, respectively). There were only a few aneurysms with medial dome projections (n=9, 2%). The posterior dome orientations accounted for about 64% of orientations. Also, many posteriorly oriented aneu-

Figure 25
Schematic drawing and 3D-CTA-reconstructionof the different PcomA origins in a relation to PcomA aneurysm: (A) separate (32%), (B) side by side (21%) and (C) a joint neck with the aneurysm (6%). Every third patient had no visible PcomA.



Morphology of the Internal Carotid Artery and the PcomA

rysms had some lateral alignment and nearly half of the PcomA aneurysms (n=202, 49%) came in contact with the medial aspect of the temporal lobe.

There were significant differences in the orientations of ruptured and unruptured PcomA aneurysms (p=0.01, 95%CI, medial orientations in one group). The orientations with largest proportion of ruptured aneurysms were superolateral (91% ruptured vs. 9% unruptured), lateral (74 vs 26%), superoposterior and posterior (73 vs. 27% respectively for both) orientations. However, after multivariable analysis, the dome orientation was not an independent risk factor associated with rupture.

PComA Origin

A typical site of the PComA origin was medial to the aneurysm and in about one third of the cases separate from the neck of the aneurysm (n=134, 32%). In the remaining cases, when the PcomA was visible, the PcomA arose at the aneurysm neck and ran close to the dome (n=88, 21%), or arose directly from the aneurysm dome itself (n=26, 6%, Figure 25). In some CTA images, with narrow PcomA, the relation between the origin and the aneurysm was impossible to identify (n=23, 6%). The remaining patients had no visible PcomA (n=142, 34%). The main types of PcomA origin were classified as follows: (A) separate (32%), (B) side

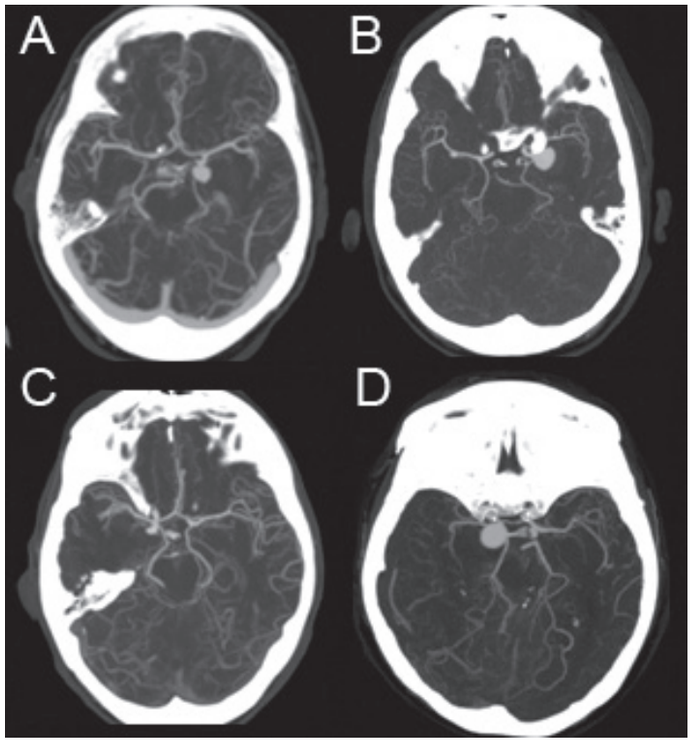


Figure 26
Axial CT images on Fetal PCA A) on patient´s left side B – C) on both sides, D) on patient´s right side.

by side (21%) and (C) a joint neck with the aneurysm (6%).

There did not seem to be relevant differences in morphology of the parent vessels: the ICA and the PcomA (length and diameter of the ICA, angle of the supraclinoid ICA, diameter of PcomA and level of its origin).

The diameter of the internal carotid artery (ICA) at the skull base seemed to be slightly smaller among ruptured aneurysms compared to unruptured aneurysms.

Vascular Anomalies Related to PcomA Aneurysms (Publication I)

Fetal PCA or Dominant PcomA

Fetal PCA, i.e., an absent or hypoplastic P1 segment with the PCA arising directly from the PcomA, was the most common anatomical anomaly; 35% of the PcomA aneurysm patients had fetal PCA (24%) or thick, dominant PcomA in addition to the PCA (11%) on the same side as the PcomA aneurysm (Figure 26 & 27). There were no significant differences in posterior communicating artery diameters when comparing ruptured and unruptured PcomA aneurysms.

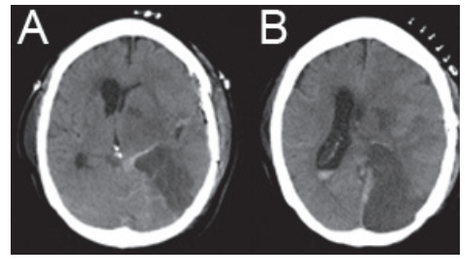
Duplication of PCA

As for another rare anatomical variation, two patients had duplication of the PCA (<1% of patients) as the posterior communicating artery never attached to the PCA but ran alongside to it to the temporo-occipital PCA region.

Morphological Parameters Related to PcomA Aneurysm Rupture (Publication I)

The morphological parameters that seemed to be significantly related to PcomA aneurysm rupture after the univariable analysis were larger aneurysm size, wider diameter of the aneurysm neck, larger aspect ratio and bottleneck factor, irregularity of the aneurysm dome and aneurysm orientation,

Figure 27
Brain infarction caused by fetal PCA occlusion.



the aneurysm's relation to the tentorium and the diameter of the ICA.

After the multivariable logistic regression, the statistical significance was retained for these independent risk factors: irregular aneurysm dome, larger diameter of the aneurysm neck, smaller diameter of the ICA at the skull base and aspect ratio >1.5 (Table 6).

The differences in diameter of the ICA were minor in millimeters, and taking into account the limitations in measurement accuracy, this parameter may not be a clinically relevant finding after all.

Irregular Aneurysm Dome

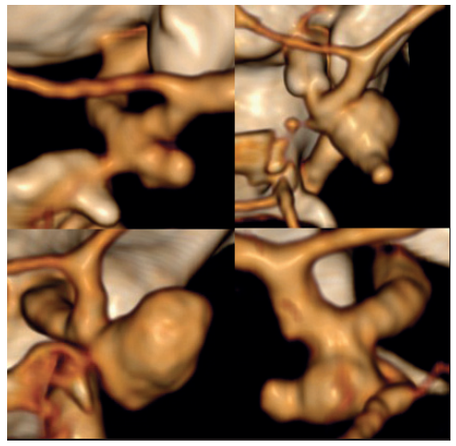
Up to 90% of the ruptured PcomA aneurysms (n=231) had irregular domes as opposed to only 34% of the unruptured ones (Figure 28). Aneurysm dome irregularity, or lobulations, was an independent factor related to rupture according to the results of the multivariable analysis. It was associated with the highest odds of rupture (OR 8.3).

Diameter of the Aneurysm Neck

For 90% of the aneurysms, the neck was 5mm or smaller (mean 3.5mm, range 1–13mm, sd ±1.5mm). Ruptured PcomA aneurysms had somewhat wider necks than unruptured PcomA aneurysms (mean neck

3.7mm vs. 3.1mm respectively, p < .001). Wider aneurysm neck was independently associated with PcomA aneurysm rupture.

Figure 28
Examples of PcomA aneurysms with irregular domes.



Aspect Ratio

Aspect ratios (length divided by neck) of ruptured PcomA aneurysms were statistically larger than aspect ratios of unruptured aneurysms (mean 2.2 vs. 1.6, < 0.001, 95% CI). The majority of the ruptured aneurysms had aspect ratio >1.5 (77%), aspect ratio ≤1 was uncommon among ruptured aneurysms (4% of all ruptured), whereas it was quite common among unruptured ones: 4% of the ruptured vs. 37% of the unruptured PcomA aneurysms had aspect ratio ≤1. This indicates that ruptured aneurysms were in general more oblong shaped than their unruptured counterparts, which were more often regular or flat. The aspect ratio >1.5 was an independent risk factor associated with rupture.

Parameter	Odds Ratio	95% CI	p value
Smooth Dome (Irregular->Smooth	0.12	0.07 – 0.22	P < 0.001
Irregular Dome (Smooth->Irregular)	7.7 (±3.2)	4.9 (±3.5)	< 0.001
Diameter of the Aneurysm Neck	1.30	1.07 – 1.61	0.012
Aspect Ratio > 1.5	2.26	1.26 – 4.04	P < 0.001
Diameter of the ICA	0.50	0.32 – 0.75	0.006

Table 6
Results of the multivariable logistic regression presenting the remaining independent risk factors associated with PcomA aneurysm rupture.

Clinical Features of PcomA Aneurysm Rupture (Publication I & II)

Presentation

Most of the PcomA patients (n=296, 76%) between 2000 and 2014 were treated because of SAH; 290 patients (74%) had classical SAH symptoms, 23 patients (6%) had oculomotor nerve palsy as the main symptom. A smaller proportion of patients were treated solely because of unruptured PcomA aneurysm(s) (n=95, 24%), most of which were detected as incidental findings (17% incidental, 3% screening, <1% epilepsy).

Severity of Bleeding

After 2000, most ruptured PcomA aneurysms caused severe SAH (Fisher grade 4) n=177, 69% of all ruptured PcomA aneurysms (Figure 29). The typical distribution of severe bleeding was SAH in the basal cisterns with intraventricular hemorrhage (n=105, 41%), temporal intracerebral hemorrhage (n=65, 26%). The rest of the PcomA aneurysm patients with severe bleeding also had subdural hematomas (SDHs) or frontal intracerebral hematomas (n=7, 3%).

Oculomotor Nerve Palsy

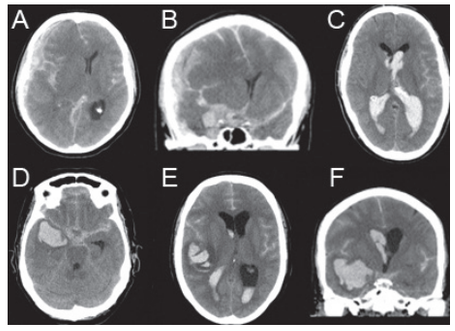
Oculomotor Nerve Palsy (ONP) was a typical symptom after PcomA aneurysm rupture: 16% of patients with ruptured PcomA aneurysm (n=102), had oculomotor nerve palsy. According to follow-up data of 44 patients, the majority or 75% of them had full recovery. The rest, 25%, had partial recovery and they were often left with occasional diplopia.

Early Rebleedings and Timing of Treatment (Publication II)

Of all patients treated for ruptured PcomA aneurysms between 1980 and 2014, the number of patients having a rebleeding before treatment was quite high (n=149, 24%), even though the majority of patients (n=582, 94%) were treated actively. The ultra-early timing of occlusive aneurysm treatment (<24h) has become more common since 2000; since then, 88% of patients were treated within 24 hours of admission to the neurosurgical unit whereas previously this proportion was 35% of patients (1980–1999).

Patients with rebleeding had a significantly worse outcome than those without rebleeding; 32% dead and 21% mRS 3–5 vs. 18% dead and 13% mRS 3–5, respectively. In multivariable analysis, however, rebreeding before treatment was not an independent risk factor for impaired outcome.

Figure 29
Axial and coronal CT scan of patients with severe bleeding after PcomA aneurysm rupture A-B) aSAH with SDH, C) aSAH with IVH, D) aSAH with temporal ICH, E-F) aSAH with temporal ICH and IVH.



Treatment Methods of PcomA Aneurysms (Publication II)

The majority of the 620 patients with ruptured PcomA aneurysm treated between 1980 and 2014, 83% (n=517), were treated by microsurgical clipping, 8% (n=49) of patients by endovascular embolization (Table 8). These were the main treatment modalities.

A few (n=10, 2%) were treated with combined techniques (microsurgical and endovascular). In the early years of the study period, two patients were treated with indirect means by carotid ligation and four patients by trapping. Two patients were treated by carotid occlusion after failed clipping. A small group of patients (n=38, 6%) was treated conservatively, most because of their poor clinical condition on admission (Table 7).

Table 7
Features of ruptured posterior communicating artery aneurysms and method of treatment

	Ruptured PcomA aneurysm (n=620)	
	n	%
Size		
Small (<7 mm)	186	30
Medium (7–14 mm)	315	51
Large (15–24 mm)	34	5
Giant (≥25 mm)	7	1
Missing	78	13
Surface of dome		
Irregular	489	79
Smooth	63	10
Not known	67	11
Morphology		
Saccular	620	100
Fusiform	1	<1
Microsurgical treatment	524	84
Clipping	517	83
Indirect methods	6	1
Endovascular treatment	49	8
Combined treatment	10	2
Reason for conservative treatment	38	6
Poor condition	22	4
Old age	2	<1
Refused	3	<1
Other	4	<1
Died before treatment	7	1

PcomA =posterior communicating artery.

Occlusion Rate and Additional Treatment (Publication II)

The postoperative angiography (DSA or CTA) was performed in 95% (n=551) of the cases. There were marked differences in radiological occlusion rates after different treatment methods. Total occlusion was 90% for clipping, 67% for endovascular and 100% for combined methods. A complete failure in occlusive treatment of the ruptured PcomA aneurysm was seen in only three patients (2 clipping and 1 coiling).

The need for immediate additional treatment was 4% for clipped aneurysms (n=19), and 12% for coiled aneurysms (n=6). In addition, seven coiled PcomA aneurysms were re-embolized during the first year of follow-up. This raises the proportion of re-treated embolized PcomA aneurysms to 27% during the first year.

Complications (Publication II)

Procedural and aSAH-related Complications

The most common procedural complications were occlusive aneurysm treatment-related ischemic lesions (15%) and artery occlusion in postoperative angiography (CTA or DSA) (10%). Occlusive treatment-related ischemic lesions included: small thalamic ischemia (6% of all treated patients, Figure 30), occlusion or thrombosis of internal carotid artery or middle cerebral artery (3%), occlusion of fetal/dom-

Figure 30
A typical postoperative lacunar, thalamic ischemia probably caused by PcomA or thalamoperforating artery compromise.

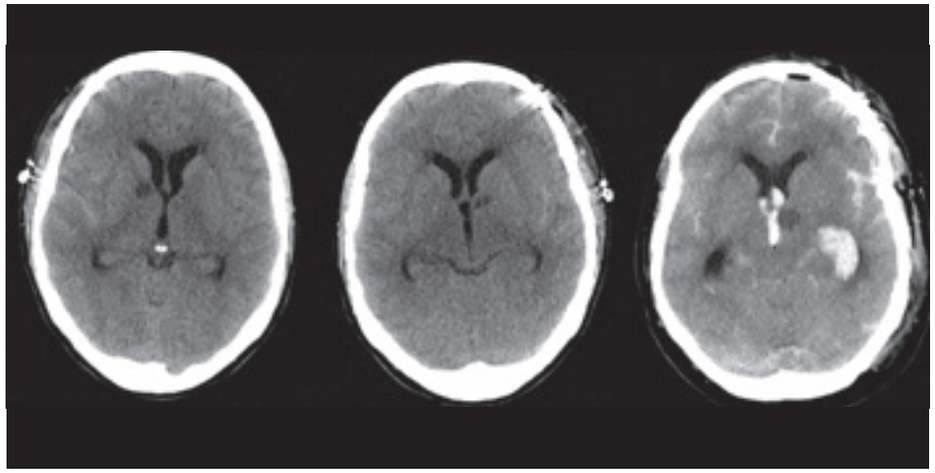


Figure 31
Patients outcome at discharge and at one year after the aSAH according to modified Rankin Score (mRS).

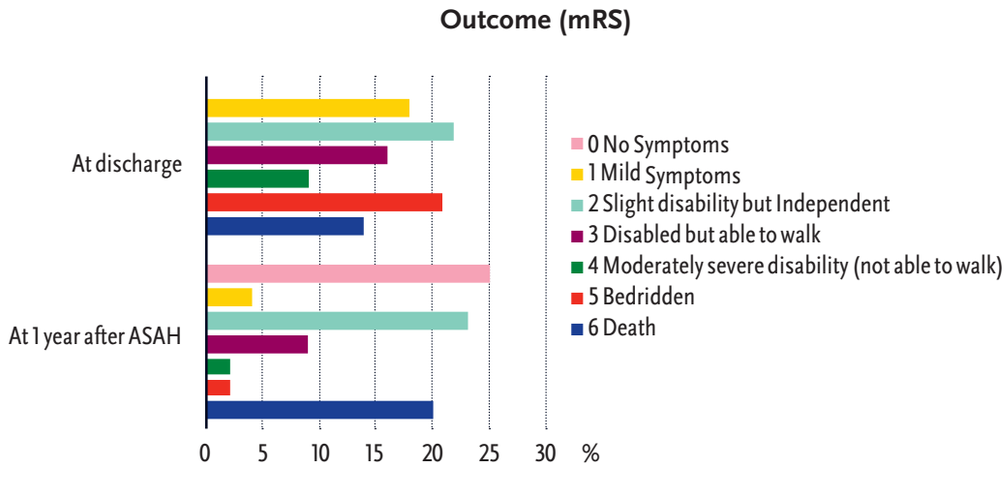


Table 8
Most Common Complications of Initial Treatment Period after PcomA Aneurysm Rupture

	Microsurgical n=517	Endovascular n=49	Combined n=10	Indirect method n=6	Total n=582
Rebleeding Before Treatment	113 (22%)	9 (18%)	3 (30%)	1 (14%)	126 (22%)
Artery Occlusion	54 (10%)	4 (8%)	0 (0%)	2 (29%)	60 (10%)
Occlusive treatment-related ischemia	80 (15%)	4 (8%)	2 (20%)	2 (33%)	88 (15%)
Postoperative Infection					
Meningitis	31 (6%)	3 (6%)	1 (10%)	0 (0%)	35 (6%)
Pneumonia	133 (26%)	17 (35%)	5 (50%)	1 (14%)	156(25%)
Septicemia	21 (4%)	2 (4%)	0 (0%)	0 (0%)	23 (4%)
UTI*	139 (27%)	15 (30%)	1 (10%)	1 (14%)	156(25%)
Wound infection	12 (2%)	0 (0%)	0 (0%)	0 (0%)	12 (2%)
Pulmonary Embolism	7 (1%)	0 (0%)	0 (0%)	0 (0%)	7 (1%)
Deep venous thrombosis	8 (2%)	0 (0%)	0 (0%)	0 (0%)	8 (1%)
Postop Cardiac Infarction	6 (1%)	1 (2%)	2 (20%)	0 (0%)	9 (2%)
Postoperative Hematoma	14 (3%)	1 (4%)	1 (10%)	0 (0%)	16 (3%)
EVD-related Hematoma**	10 (2%)	2 (4%)	0 (0%)	0 (0%)	12 (2%)
Hydrocephalus requiring a shunt	77 (15%)	9 (18%)	3 (30%)	0 (0%)	89 (15%)
Delayed Vasospasm	103 (20%)	6 (12%)	0 (0%)	2 (33%)	111 (19%)
Death within 1 month	49 (9%)	7 (14%)	2 (20%)	3 (43%)	61 (10%)

*Urinary tract infection **Extra-ventricular drainage
% are presented within each treatment group

Table 9
Independent Risk Factors for Unfavorable Outcome (mRS >2) at 1 Year

	p value, Chi-squared test	Odds Ratio/ Risk of Impaired Outcome
Age Group	< .001	
<50		1.0
50 – 65,		1.7
>65		7.2
Poor Preop Grade	< .001	
HH3		1.8
HH4-5		4.9
ICH/SDH related to aSAH	< .001	2.5
Artery Occlusion in Postoperative Angio	< .001	5.0
Delayed Cerebral Vasospasm	< .001	2.0
Occlusive Aneurysm treatment-related Ischemia	< .001	3.7
Hydrocephalus requiring a Shunt	< .001	2.4

inant PcomA or anterior choroidal artery (AchA) (2%) and other treatment-related ischemia (5%).

Other aSAH-related complications included infections (pneumonia 25%, urinary tract infection 25%), symptomatic delayed cerebral vasospasm (19%) and hydrocephalus requiring ventricular drainage (16%) or a shunt later on (15%). Thromboembolic events were a minor problem during the initial treatment period (Table 8). Most patient who died because of aSAH (17%) died during the first month after the bleeding.

Outcome after Treatment of Ruptured PcomA Aneurysm

Recovery at 1 Year after Treatment

Most of the patients made good recovery at 1 year after rupture and treatment of PcomA aneurysm (mRS0-2 n=384, 62%, Figure 31). Altogether 416 patients (67%) were able to return home directly from a neurosurgical unit or after a rehabilitation period. Up to 84% of the under 50-year-olds recovered home after rehabilitation. The outcome data of all actively treated patients are presented in Table 10. Patients who recovered well often still reported neuropsychological symptoms, e.g. abnormal tiredness or difficulties in memory functions or concentration, at three-month and one-year check-ups.

Even patients with severe disabilities at discharge usually made significant im-

provement neurologically during the first year (mRS4-5: 31% at discharge vs. 4% at 1yr FU). A fairly small proportion of patients were left severely disabled (n=27, 4% mRS4-5 not able to walk or bedridden).

Mortality

Of all the patients with ruptured PcomA aneurysm (both active and conservative treatment groups), 20% died during the first year (n=127). The most common cause of death was the initial aSAH (n=118, 93% of all deaths). Those who died because of aSAH could be divided into subgroups according to contributing factors: severe initial bleeding (n=42, 33%), additional brain infarction (n=33, 26%), severe vasospasm (n=6, 5%), early rebleeding (n=18, 22%), delayed other complication related to aSAH and poor condition (n=19, 15%).

Risk Factors for Impaired Outcome

After the multivariable logistic regression, the independent risk factors for impaired outcome after PComA aneurysm rupture turned out to be poor preoperative clinical condition (HH), older age (>65 yrs) and ICH or SDH after aneurysm rupture of the preoperative factors and artery occlusion in postoperative angiography, delayed cerebral vasospasm, occlusive aneurysm treatment-related brain infarction and hydrocephalus requiring a shunt of the postoperative factors (Table 9).

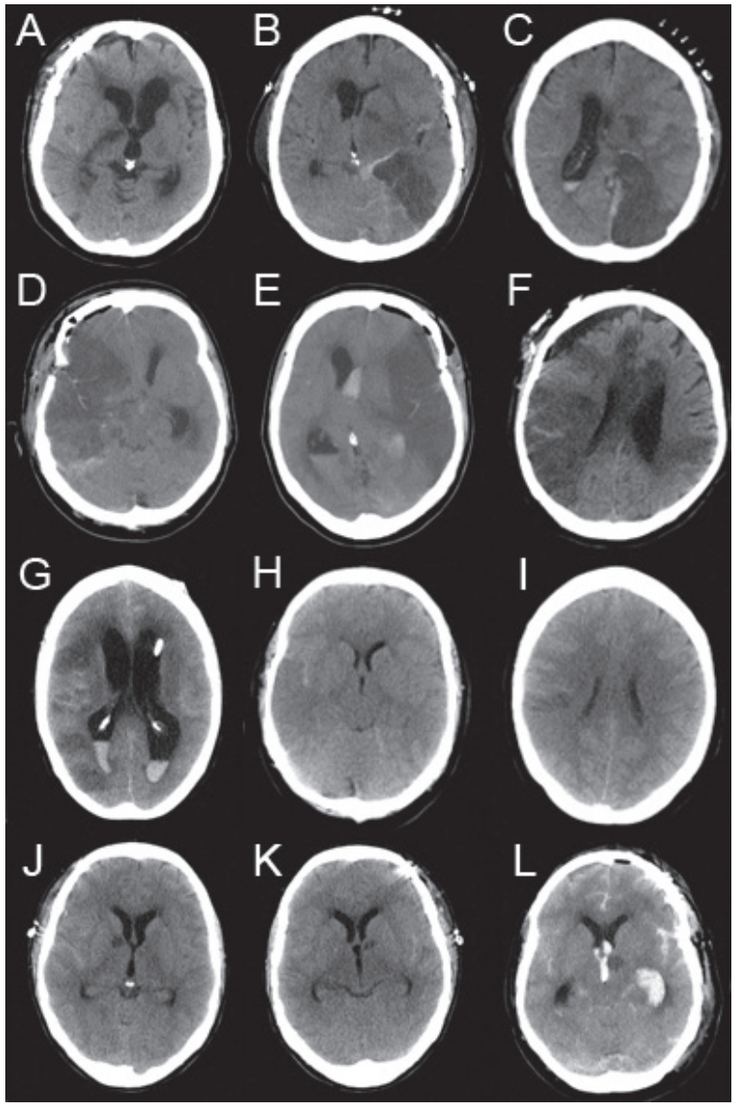
The highest odds of impaired outcome were related to 1) age over 65 (OR 7.2), 2) artery occlusion in postoperative angiography (OR 5.0.) 3) poor preoperative clinical condition, HH4-5 (OR 4.9) and 4) occlusive-treatment related brain infarction (OR 3.7) (Table 9).

Table 10
Occlusive treatment-related ischemia according to preoperative clinical condition of treated patients

Preoperative Clinical Condition Occlusive Treatment- related Ischemia	HH1-2 n	HH3 n	HH4 n	HH5 n	Total 583
ICA or MCA occlusion*	7	6	2	0	15 (3%)
Fetal/Dominant PComA or AntChA occlusion**	1	1	6	3	11 (2%)
Thalamic Ischemia	15	8	11	4	38 (6%)
Angiography related ischemia	0	1	1	0	2 (<1%)
Other treatment related	9	6	7	1	23 (4%)
TOTAL	32	22	27	8	89 (15%)

*ICA Internal carotid artery, MCA Middle cerebral artery
**AntChA Anterior Choroidal Artery

Figure 32
Ischemic complications after occlusive treatment of ruptured PComA aneurysm: A) infarction of the internal capsule after AChA occlusion, B–C) temporo-occipital infarction after fetal PCA occlusion, D–E) malignant MCA area infarction after ICA or MCA occlusion, F–G) multiple bi-hemispheric infarctions after severe vasospasm, H–I) right MCA area cortical ischemic lesion after embolic complication of coiling, J–L) small thalamic infarctions after PComA or thalamo-perforating artery sacrifice.



Age and Hydrocephalus after PComA Aneurysm Rupture

On admission, 42% (n=258) of patients with ruptured PComA aneurysm had dilated ventricles. About half of patients with dilated ventricles (n=108, 17%) needed ventricular drainage to treat the condition. Nearly as many (n=90, 15%) received a permanent shunt later on. About half of the patients requiring a shunt had had an EVD earlier (n=47), the others developed hydrocephalus later on. Hydrocephalus requiring an extraventricular drainage (EVD) was not an independent risk factor for impaired outcome.

Post-aSAH hydrocephalus was more common among the elderly patients when compared to younger age groups (permanent shunt 7%, 24% and 34% respectively for <50-, 50–65- and >65-year-olds). The differences between age groups were prominent. Over one third of the patients whose age was over 65 years required a shunt during the follow-up. Both older age and hydrocephalus requiring a shunt were independently associated with higher odds of impaired outcome (Table 9).

Preoperative Clinical Condition

Poor preoperative clinical condition (HH4-5) was an independent risk factor for impaired outcome. Nearly half of the poor grade patients died (n=74, 49%). However, some made good recovery at 1 year (mRS0-2: n=39, 26%; mRS3: n=25, 17%). Patients in good clinical grade after the bleeding were still exposed to occlusive aneurysm treatment-related risks, and treatment-related brain infarctions were prominent in good grade patients as well (Table 10).

ICH or SDH after aneurysm rupture

Patients with intracerebral (ICH, n=71, 11%) or subdural hematomas (SDH, n=24, 4%) had an elevated risk of impaired outcome (Table 9). IVH related to aSAH was not an independent risk factor. Patients with ICH or SDH or both were often in poor clinical condition on admission (HH4-5: n=58, 61% of patients with hematomas) and they were mainly treated surgically (n=79, 83%), which gave the opportunity for removal of the hematoma when needed.

Delayed Cerebral Vasospasm

Delayed cerebral vasospasm and ischemia (clinical symptoms and radiological findings) were detected and treated in 18% (n=111) of the patients. In about one third of these patients (n=38) the vasospasm was classified as severe, with deterioration of consciousness and focal deficits. Only one fifth of patients who got treatment for vasospasm (n=23, 4% of all) developed visible ischemic lesions caused by the condition. It is possible though, that regarding patients who had ischemic lesions of unknown origin (n=62, 10% of treated patients), some were related to delayed cerebral vasospasm and ischemia but were not verified.

Occlusive Treatment-related Brain Infarctions

Artery occlusions and brain infarctions were prominent complications also among young patients. Of all actively treated PComA patients, 10% of the patients (n=60) had artery occlusion according to the postoperative angiography (Table 4). A smaller number (n=26, 4%) had postoperative brain infarctions related to main artery occlusion or thrombosis (Figure 32). Also, some of the deep, thalamic infarctions (7%) might be related to PComA compromise, others to damage of small perforant arteries not visible in angiography. Even though there were some correlation between the groups of artery occlusions and occlusive-treatment related infarctions, they were both estimated to be independent risk factors for impaired outcome as well (Table 9).

Table 11

Characteristics of 3078 aSAH patients who survived a minimum of one year (range 1 – 33yrs).

	Total n (%)
Sex	
Female	1700 (55%)
Male	1378 (45%)
Number of aneurysms	
1	2176 (71%)
2	589 (19%)
3	211 (7%)
4	68 (2%)
>4	34 (1%)
Location of ruptured aneurysm	
ICA	593 (19%)
MCA	1047 (34%)
AcomA & A1	1092 (36%)
DACA	138 (5%)
Posterior Circulation	206 (7%)
Active treatment	
Yes	3033 (99%)
No	45 (1%)

	Total n (%)
Preoperative HH	
I	736 (24%)
II	1069 (35%)
III	691 (22%)
IV	483 (16%)
V	98 (3%)
GOS at 1 year *	
5 Good Recovery	1449 (37%)
4 Moderate Disability	863 (22%)
3 Severe Disability	479 (12%)
2 Persistent vegetative state	22 (1%)
1 Death	871 (22%)
Vital status at the end of follow-up	
Alive	2107 (68%)
Dead	971 (32%)

* includes patients who died during the first year after aSAH
ICA Internal carotid artery, MCA Middle cerebral artery, AcomA Anterior communicating artery, A1 The first segment of anterior cerebral artery, DACA Distal anterior cerebral artery

Table 12
The most common causes of death in 1-year survivors of aSAH, and in the general Finnish population.

Cause of Death	Study Patients All / <65-year-olds	General Finnish Population All / <65-year-olds
Cardiovascular disease	26% / 26%	30% / 19%
Cancer	22% /24%	23% / 28%
Cerebrovascular disease	13%/ 12%	9% / 4%
Initial aSAH and sequelae	12% / 8%	<0,5% /–

Long-Term Excess Mortality after aSAH

Long-Term Mortality and Causes of Death (Publication III)

A total of 971 patients (32%) of the 3078 1-year survivors after aSAH died during long-term follow-up (Table 11). The most common causes of death were cardiovascular disease (n=249, 26%) and cancer (n=215, 22%). Patients younger than 65 years also had cardiovascular disease as the leading cause of death (n=210, 24%). There was a total of 162 deaths (17% of all) caused by aSAH over the entire time period. The majority of those (n=113, 70%) were related to the initial aSAH. Deaths caused by cerebrovascular disease other than aSAH were also common in the study group (n=26, 16% for ≥65 years and n=95, 12% <65 years). The common causes of death in the study population and among the general Finnish population have been presented in Table 12.

Recurrent aSAH (Publication III)

Rebleeding during the follow-up period was the cause of death in 24 patients (2%) and 25 patients (3%) died due to the rupture of another aneurysm. The incidence of lethal recurrent aSAH was 100/100,000 person-years. The incidence was 68/100,000 for patients with a single aneurysm and 185/100,000 for patients with multiple aneurysms. This means that patients with multiple aneurysms had a three-fold risk of having lethal rebleeding during the follow up when compared to patients with a single aneurysm (Huhtakangas et al. unpublished results).

Long-Term Excess Mortality and Risk Factors (Publication III)

There was constant excess mortality throughout the whole study period among the study population compared to the matched general population (Figure 33). Cumulative relative survival ratio (RSR) was 0.83 at 20 years and 0.68 at 30 years (95% CIs 0.80–0.85 and 0.63–0.73). This indicates an excess mortality of 17% and 32% at 20 and 30 years respectively. Even young patients and patients with good recovery at 1 year showed excess mortality in the long run (about 20% at 30 yrs).

Risk factors for long-term excess mortality included (i) multiple aneurysms; (ii) age (especially >60 years); (iii) poor preoperative clinical condition; (iv) conservative treatment; and (v) unfavorable clinical outcome at one year.

Age

Patients over 60 years of age (n=583) had markedly higher excess mortality than <45-year-olds (n=1207) (20-year cumulative

Figure 33
Long Term Excess Mortality after aSAH shown by cumulative RSRs of 3078 aSAH patients

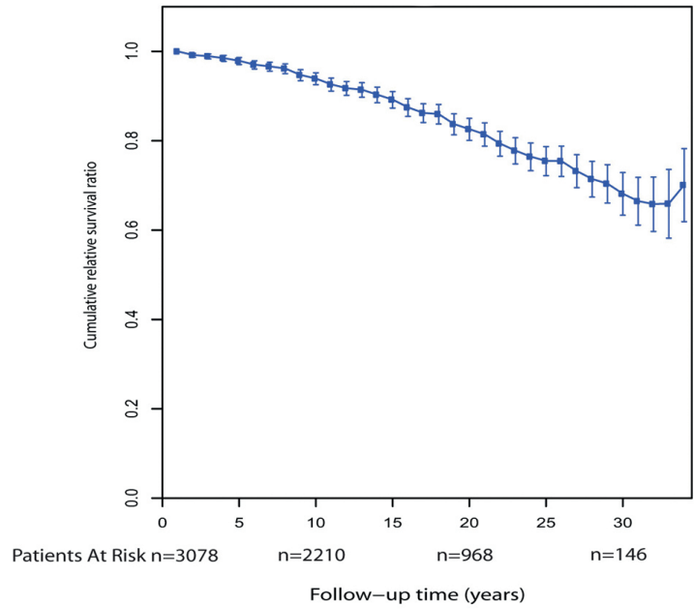
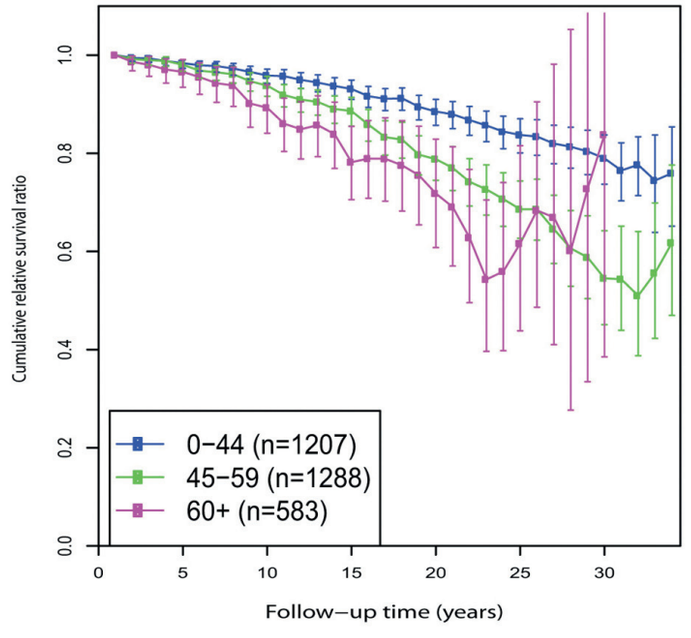


Figure 34
Cumulative RSRs of different age groups in a long term follow-up.



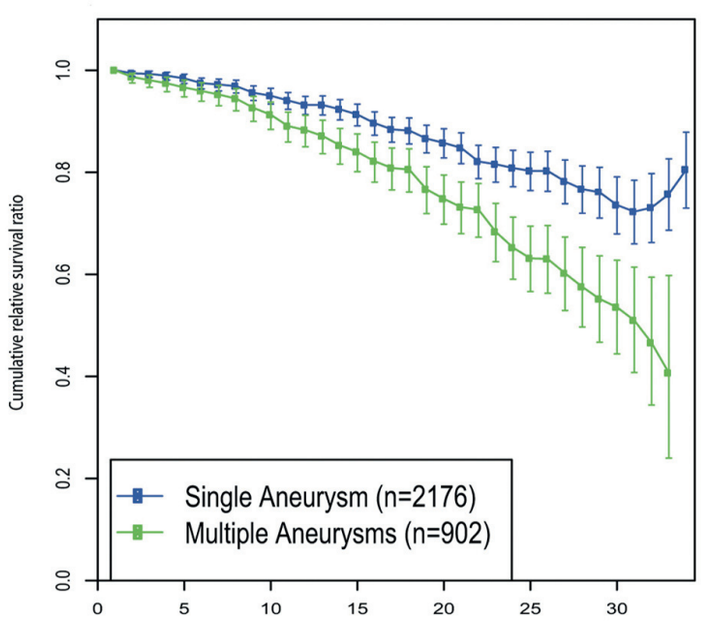


Figure 35
Long-term excess mortality, presented by cumulative RSRs, was more evident among aSAH patients with multiple aneurysms when compared to patients with a single aneurysm.

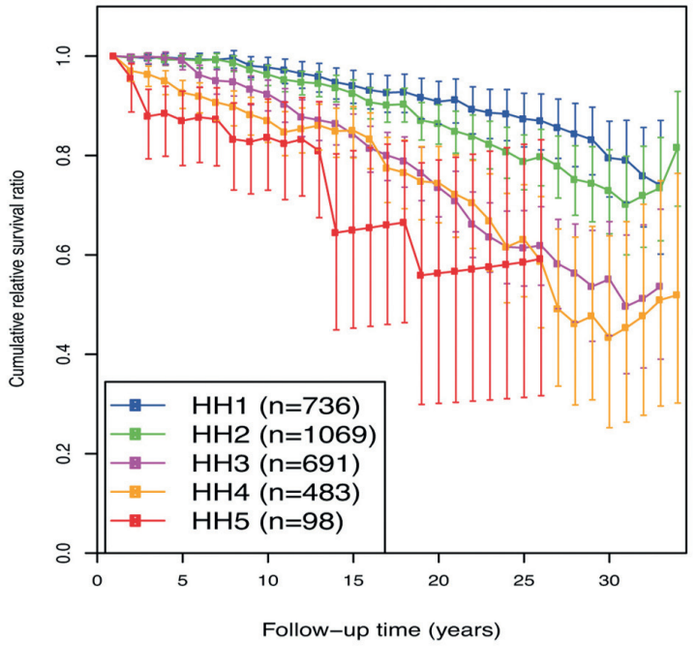


Figure 36
Cumulative relative survival ratios (RSRs) according to patients´ preoperative clinical condition (presented according to Hunt & Hess groups 1 – 5).

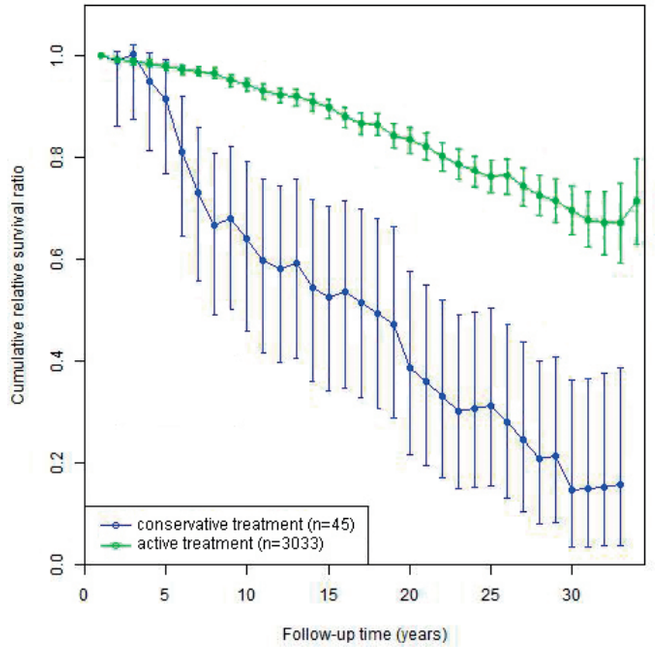


Figure 37
The highest long-term excess mortality in the long run was related to aSAH patients who were treated conservatively. Cumulative RSRs of conservative and active treatment groups.

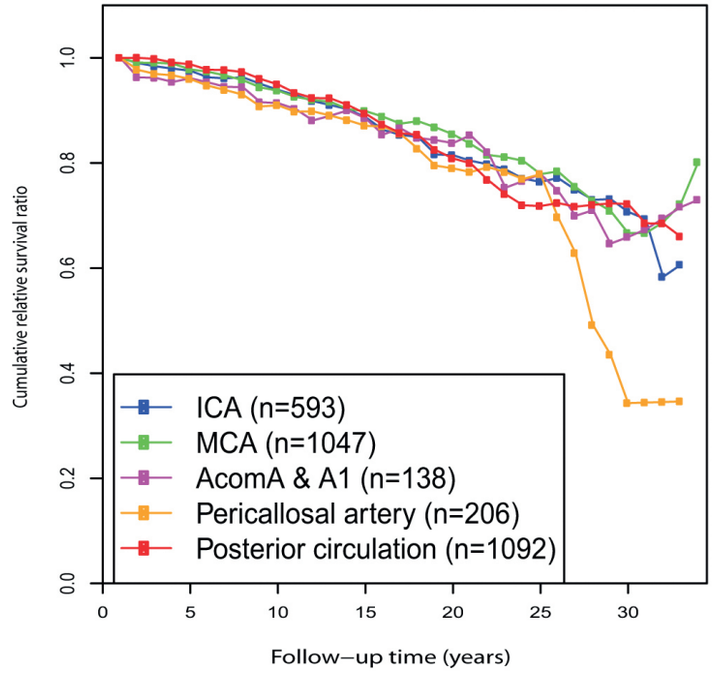
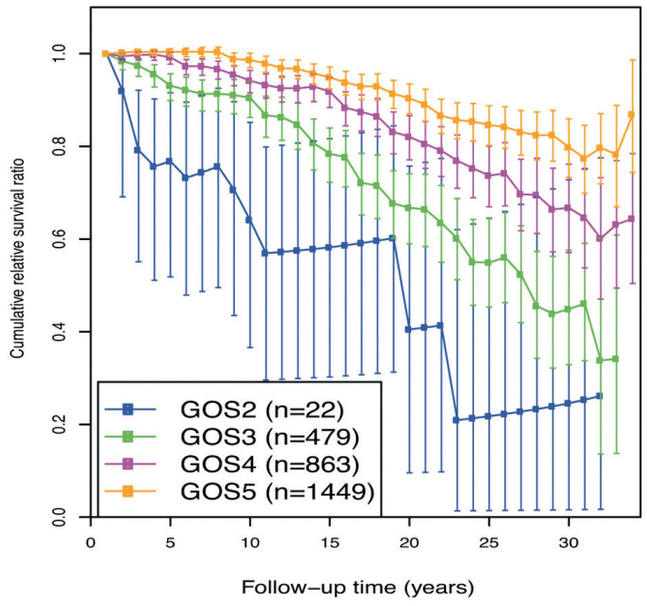


Figure 38
The cumulative RSRs of patients divided into groups by aneurysm location.

Figure 39
The cumulative RSRs of aSAH patients according to their clinical outcome at 1yr after aSAH presented by GOS score 2-5. Even patients with the best outcome (GOS5) started to show excess mortality in the long run.



RSR 0.72 vs. 0.89, 95% CI 0.61–0.83 vs. 0.86-0.91 respectively). However, younger patients (age <45 years) also had significant long-term excess mortality, 21% in 30 years, compared to their matched counterparts in the general population (30-year cumulative RSR 0.79, 95% CI 0.74–0.84). Cumulative relative survival ratios (RSRs) of different age groups are presented in Figure 34.

The most common causes of death in young patients were cardiovascular disease (n=52), cancer (n=47), aSAH (n=46) and other cerebrovascular disease (n=18) accounting for 22%, 20%, 19% and 8% of all causes of death in this age group respectively. The proportion of lethal SAH from another aneurysm (n=14, 6% of all causes of death) was greater among young patients than others.

Multiple Aneurysms

Patients with a single aneurysm at the beginning of the follow-up (n=2176) had a better survival rate than patients with multiple aneurysms (n=902) (30-year cumulative RSR 0.74 vs. 0.54, 95% CI 0.68–0.79 vs. 0.44–0.63, Figure 35). New and lethal SAH from another aneurysm was more common in patients who had multiple aneurysms at the start of follow-up than for single aneurysm patients who subsequently developed de novo aneurysms (n=14, 20% vs. n=11, 12% of patients with SAH related cause of death). Incidences of other vascular causes of death in these two groups were practically the same: cardiovascular disease 24% (multiple) vs. 26% (single), and other cerebrovascular causes 12% vs. 12%.

Preoperative Clinical Condition

Patients with severe neurological impairments before treatment had significantly higher excess long-term mortality than those with mild symptoms only. Poor grade patients (HH4-5) showed excess mortality from the beginning of the follow-up, and it continued. Patients with better preoperative condition (HH1-3) started to show significant excess mortality later in the follow-up. Even patients with HH grade 1 had clear excess mortality, which started to show after eight years of follow-up. The excess mortality at 30 years for HH1 patients was 20% (cumulative RSR 0.80, 95% CI 0.72–0.87), for HH2: 27% (cRSR 0.73, 95% CI 0.64–0.81), for HH3: 45% (cRSR 0.55, 95% CI 0.44–0.67) and for HH4: 57% (cRSR 0.43, 95% CI 0.25–0.64, Figure 36).

Conservative Treatment

Conservative treatment resulted in very poor long-term survival: cumulative RSR at 20 years was 0.39 (95% CI 0.22–0.58). The 20-year cumulative RSR for actively treated patients was 0.83 (95% CI 0.81–0.86, Figure 37).

The conservatively treated patients were in worse clinical condition upon admission to the hospital (HH4-5: 44%, HH3: 31%) than the actively treated patients (HH4-5: 19%, HH3: 22%). The proportion of lethal rebleedings was higher in the conservatively treated group than in the active treatment group (n=5, 11% of conservatively treated vs. n=19, less than 1% of actively treated patients).

Aneurysm Location and Gender

The aneurysm location did not affect the long-term survival (Figure 38). A greater portion of aSAH patients who had ruptured posterior circulation aneurysm died during the first year after aSAH compared to those with ruptured anterior circulation aneurysm (38% vs. 26%). However, there were no significant differences between the different aneurysm locations at later times during the follow-up, as shown in Figure 38. PComA aneurysm patients are included in Internal Carotid Artery (ICA) aneurysms. The excess mortality was 20% at 20 years for patients with an ICA-PComA aneurysm (cRSR 0.80, 95% CI 0.74–0.86, Huhtakangas et al. unpublished results).

The gender of the patients did not affect the long-term excess mortality either: at 20 years, the excess mortality was 17% for men and 18% for women, and at 30-years it was 32% for both.

Outcome at One Year

Patients who had serious disabilities at one year after the aSAH event also had greater long-term excess mortality compared to patients with good recovery (Figure 39). Interestingly, even patients with excellent recovery (GOS5) at one year had notable long-term excess mortality compared to their matched counterparts in the general population, 20% in 30 years (30-year cumulative RSR 0.80, 95% CI 0.73–0.86). This difference did not start to show until after eight years of follow-up. The most common causes of death in this group were cardiovascular disease (30%) and cancer (27%). The proportion of aSAH related deaths in this group of patients with best recovery was the lowest (9% for GOS5 patients; 12% for GOS4 patients and 22% for GOS3 patients).

Discussion

Posterior Communicating Artery Aneurysms
Main Morphological Features and Clinical Aspect (Publication I)

Size

Aneurysm size has been strongly related to the risk of rupture [125, 188, 192, 267, 272, 123]. Ruptured aneurysms tend to be larger than unruptured ones. This was seen in our results in publication I as well, even though a notable proportion, 38%, of the ruptured PComA aneurysms were small (<7mm). Thus, size may not be the best indicator for which PComA aneurysms may rupture.

Large or giant PComA aneurysms were infrequent. Also, in the PComA series of Yasargil, there were only a few large PComA aneurysms (2% of all 173). It has been speculated that PComA aneurysms seldom get to grow large because of early symptoms caused by the close proximity of the oculomotor nerve [276]. Another explanation could be that PComA aneurysms have a greater rupture risk compared to other locations of anterior circulation aneurysms, so they do not reach a large size before rupturing [188, 272]. Our results suggested that in addition to size, other morphological features like the size of the aneurysm neck and shape and irregularity of the dome may be useful parameters.

One aspect related to especially larger aneurysms were the relations to surroundings and adhesions that PComA aneurysms may have. These should be taken into account when planning and carrying out microsurgical procedures. Potential points of adhesions were posterior clinoid process (21% of PComA aneurysms made a contact), the dome reaching close to the base of the skull (15%), adherence to tentorium or reaching below it (26%), and contact with the mesial temporal lobe (49%).

PComA Origin and its Variants

The origin of the PComA with respect to the aneurysm neck and dome is a clinically important feature for both endovascular and microsurgical treatment [17, 30, 157, 232, 276, 279]. In about a third of the cases, the PComA origin was separate from the neck of the aneurysm or the vessel coursed away from the aneurysm dome. This would be the optimal configuration from the treatment point of view.

In more complicated cases, 28% of the patients, the PComA arose just at the aneurysm neck running close to the dome or from the dome directly. In these configurations, the risk of accidental occlusion of the PcomA might be higher, irrespective of the treatment method. Especially in cases with the PComA arising directly from the aneurysm dome, coiling or clipping is usually not possible without either compromising the posterior communicating artery or leaving a neck remnant. This may lead to suboptimal occlusion and a need for additional follow-up.

Up to about one third of ruptured PComA aneurysms had fetal or dominant PComA on the side of the aneurysm, where preserving the artery is highly important as its obliteration causes a substantial risk of PCA area infarction and neurological sequelae [279]. A duplication of the PCA probably should be preserved equally carefully as the fetal type PCA. The diameter of the PComA was not statistically related to rupture, but it has evident significance in clinical work. A compromise of the PComA may also cause a thalamic infarction [17, 43].

Dome Orientation

Inferoposterior dome orientation was the most common projection among PComA aneurysms (42%). Orientations with largest proportion of ruptured aneurysms were superolateral (91% ruptured vs. 9% unruptured), lateral (74 vs 26%), superoposterior and posterior (73 vs. 27% respectively) orientations. So most ruptured aneurysms had inferoposterior dome orientation.

Two earlier studies suggest that lateral or superolateral orientations of PComA aneurysms might be high-risk orientations regarding the rupture [180, 251]. Also, one earlier publication reported that a larger inflow angle, which can be associated with more superior PComA aneurysm dome orientation, was considered to be related to aneurysm rupture risk [175]. Our results did not clearly support these earlier findings. Even though there were larger proportions of ruptured aneurysms in superior dome orientations, the superior orientations were low in total numbers, which may affect the statistical result: all in all, the dome orientation was not an independent risk factor related to rupture according to the results of the multivariable analysis.

The aneurysm dome orientation is an important factor in occlusive aneurysm treatment. Posterior orientations of the PComA aneurysm dome accounted for 64% of all orientations in publication I. Posterior orientations may be more challenging surgically than the more lateral ones. A recent Japanese study by Fukuda et al. suggested that PComA aneurysms with posterior orientation have a higher incidence of intraoperative rupture and procedure-related infarctions and required complex clipping more often than those with a lateral orientation [73]. With the posterior dome orientation, visualization of the neck and the dome of the aneurysm may be obstructed by the internal carotid artery. Also, the perforators arising from both the ICA and PComA are more difficult to identify and secure. The microsurgical treatment of most PComA aneurysms may not be such a simple procedure as some may assume, which is discussed in another publication on complexity of treatment of PComA aneurysms [232]. The aneurysm dome orientation has less clinical significance in endovascular treatment.

Morphology and the Risk of Rupture (Publication I)

The independent risk factors associated with PComA aneurysm rupture, after the multivariate logistic regression, were the irregular aneurysm dome, larger diameter of the aneurysm neck, smaller diameter of the ICA at the skull base and aspect ratio >1.5. Considering the measurement accuracy, and only slight differences in mean values, we estimated the ICA diameter might not be a clinically significant finding. The rest may be useful in assessment of the rupture risk in unruptured PComA aneurysms with some limitations.

Irregularity

As much as 90% of the ruptured PComA aneurysms (n=231) had irregular domes as opposed to only 34% of the unruptured ones. This finding is in line with a publication on morphology of all aneurysm locations (92% irregular shapes for ruptured, 22% for unruptured aneurysms) [168]. The aneurysm dome irregularity or lobulations have been associated with rupture risk [188, 168, 180]. As most ruptured aneurysms are found as a result of bleeding, we are not definitely sure, if this morphological factor precedes bleeding and is a risk factor for bleeding or if it is a result of bleeding. When considering the theory of aneurysm wall pathobiology and the gradual degenerative and inflammatory process [257, 151, 71, 130], it seems probable that an aneurysm wall becomes mechanically more fragile prior to rupture. This includes the endothelium undergoing severe dysfunction and potentially formation of thrombus, over time, the thrombus attracts inflammatory cells and may become organized. It is possible that this process is seen as irregularity of the aneurysm wall in the angiography, and thus likely seen already prior to rupture.

Neck

The neck of a PComA aneurysm is typically narrow in comparison to its dome, which means the morphology is often suitable for both microsurgical and endovascular treatment. A larger aneurysm neck diameter seemed to be related to a higher incidence of rupture, while the wider aneurysm neck is an independent risk factor. This finding was similar to the results reported by a publication on PComA aneurysm morphology a few years earlier [102]. The underlying mechanism is not clear, but it may be related to flow dynamics. The wider aneurysm neck may allow an increased flow into the aneurysm dome, which may lead to changes in the wall shear stress.

Aspect Ratio

Most ruptured PComA aneurysms had larger aspect ratios and bottleneck factors than unruptured aneurysms, meaning they often were more oblong or rotund shaped with a narrower neck compared to the dome. In addition to describing the shape of the aneurysm, the aspect ratio also seems to be related to the aneurysm rupture. However, there are limitations to using this parameter in everyday practice, as we do not know where the clinically significant threshold values lie. In the present series, an aspect ratio >1.5 was an independent risk factor associated with rupture, which seems to be in line with previous articles evaluating the aspect ratio (or dome to neck ratio) and the rupture risk [192, 267, 153].

Limitations Related to Evaluation of Morphology and the Risk of Rupture

All present studies on PComA aneurysms study the morphology, comparing unruptured and ruptured aneurysms, which may not be an optimal setting. As ruptured aneurysms are found as a result of bleeding,

which in theory may change the morphology, we do not know for sure whether the morphological factors related to rupture also predict the rupture or only form as a result of the rupture. On the other hand, unselected natural history series are impossible to carry out nowadays to study the morphology regularly prior to rupture. Considering the knowledge that we already have, for ethical reasons, high-risk lesions will be treated prophylactically and prospective natural history series would become highly selected. Even though the most optimal setting from the researcher´s point of view may not be reached, these studies provide valuable information, and the bigger picture will emerge piece by piece. This is a limitation is encountered at times in clinical research.

Treatment and Outcome after PComA Aneurysm Rupture (Publication II)

Of the 620 patients after PComA aneurysm rupture, 83% were treated by microsurgical clipping and 8% by endovascular coiling, 2% with combined, 1% with indirect surgical methods and 6% conservatively. These methods represented the department policy in the study period. There were differences in radiological occlusion grades (90% of patients for clipping, 67% for endovascular treatment, and 100% for combined methods), but no lethal rebleedings occurred during the first year in either treatment group after active occlusive treatment.

Publication II presented that most patients make a good recovery at 1 year after treatment, including many of the patients who had significant disabilities at discharge. However, a large proportion of PComA patients were in poor clinical grade preoperatively (25% of all, 38% of the patients treated after 2000), and occlusive treatment-related complications, especially artery occlusions (10%) and treatment-related brain infarctions (15%), were more frequent than expected regardless of the treatment method.

Risk Factors for Impaired Outcome after PComA Rupture (Publication II)

The independent risk factors for impaired outcome after PComA aneurysm rupture were poor preoperative clinical condition, older age, ICH or SDH after aneurysm rupture, artery occlusion in postoperative angiography, symptomatic delayed cerebral vasospasm, occlusive aneurysm treatment-related brain infarction, and hydrocephalus requiring a shunt. Artery occlusions and treatment-related brain infarctions as independent risk factors were new findings. These complications were seen after each treatment modality even though comparisons between different modalities were not made. The other risk factors were mainly in line with the detected risk factors for impaired outcome after aSAH found by previous studies [74, 239, 139, 203].

Intracerebral or Subdural Hematomas

Ruptured PComA aneurysms may cause temporal ICH (15–26%) or SDH (3–4%, publication I–II), factors that increased the risk of impaired outcome. These results are similar to those in an earlier study on aneurysmal ICHs, which stated that the poor functional outcome is independently associated with occurrence of ICH and its volume [118]. The severity of the initial bleeding is something we have quite few possibilities to act on. A recent publication on aneurysmal ICHs reported that ICHs might be predictable according to location and size of the aneurysm and vascular risk factors (hypertension, diabetes mellitus and use of aspirin), which increase the risk of ICH or its size [118]. This might offer a way either by actively treating these vascular risks or those aneurysms available for prophylactic treatment to prevent large ICHs. This is yet theoretical, since a minority of ruptured aneurysms has been detected prior to rupture. Fast diagnosis and transfer to a neurosurgical unit as well as effective and active treatment of elevated intracranial pressure prior to hematoma evacuation are factors that should be highlighted in this group of aSAH patients.

Delayed Cerebral Vasospasm and Ischemia

Although there are promising results indicating that with modern treatment, delayed cerebral vasospasm may not increase in-hospital mortality among aSAH patients [154], it still is a significant cause of morbidity [74]. In our publication II, symptomatic delayed cerebral vasospasm was associated with two-fold risk of impaired outcome at one-year follow-up. The effect of vasospasm treatment on outcome could not be assessed in this study. The efforts to improve the treatment of cerebral vasospasm are still a topical issue. Several medical therapies have been and are being investigated [212, 6, 8].

Occlusive Treatment-related Brain Infarctions

The most common occlusive treatment related brain infarctions were lacunar, thalamic ischemia (7%) and artery occlusion related ischemia (4%). They concerned also young patients and those in initially good condition. These complications occurred throughout the whole follow-up period. Previous studies on the treatment of PComA aneurysms have reported a moderate number of lacunar infarctions (5%) and severe bleeding or spasm-related neurological complications (7%), also seen in the results of publication II, but only two cases of ICA or MCA artery occlusions [73, 255, 276, 232]. On a yearly basis, artery occlusions were infrequent in our series as well, but a large patient cohort pooled together brought forward these risks that may have seemed minimal in earlier, smaller cohorts.

Vessel Occlusions

The proportion of main vessel occlusions in the postoperative angiography were higher than expected (10% in the microsurgical and 8% in the endovascular treatment group). This finding highlights one of the goals of aneurysm treatment: the need for preserving the normal vasculature, including the posterior communicating artery, in addition to occluding the aneurysm. The occlusion of the main artery was one of the independent risk factors for impaired outcome with a five-fold odds of unfavourable recovery. This might be a modifiable factor nowadays with more versatile treatment strategies.

It seems that efforts should be made to meticulously preserve the posterior communicating artery, even with other than fetal PComAs. Even though, there are publications on PComA sacrifice that indicate the risk of infarction seems small in the presence of P1 [60, 137], our results did not support these earlier results. The sacrifice should be considered as suboptimal and potentially risky solution causing a risk of not only a PCA area infarction but also a risk of tuberothalamic infarctions. Intraoperative indocyanine green (ICG) videoangiography, intraoperative Doppler sonography and, especially in complex cases, intraoperative catheter angiography offer useful means to evaluate patency of the adjacent arteries during a microsurgical procedure [92, 224, 253, 44, 107].

Age and Chronic, post-aSAH hydrocephalus

The age of over 65 seemed to cause the highest odds of impaired outcome (OR 7.2), even higher than poor clinical condition on arrival to the hospital. Elderly patients were more prone to have disabilities at 1-year after aSAH (mRS 3–5: 23% of >65-year-olds vs. 8% of <50-year-olds), and they more often needed a permanent shunt to treat post-aSAH-hydrocephalus (34% of treated >65-year-olds vs. 7% of <50-year-olds). Also, the need for permanent shunt was associated with impaired outcome.

Several earlier publications have shown that chronic post-aSAH hydrocephalus is related to significant morbidity and readmissions to hospital [52, 280, 85, 52, 1, 109, 204]. Potential reasons for an impaired outcome after the need for permanent CSF diversion have been presented in a recent publication: elevated intracranial pressure, injury from catheter misplacement, re-hemorrhage and shunt infections [74]. The aging brain might also be too fragile to recover after accumulation of cerebrovascular burdens such as primary aSAH, hydrocephalus and potential complications or earlier degenerative processes or angiopathies.

Other Challenges Related to Treatment

The risk factors for impaired outcome expose patients to unfavourable recovery and are challenges that have not yet been defeated. Other challenges were suboptimal occlusion grades after endovascular treatment of a PComA aneurysm and early rebleedings before occlusive treatment, which, even though not independent risk factors, may be associated with increased morbidity or mortality.

Early Rebleedings

One challenge according to our results was the number of early rebleedings before occlusive treatment of the ruptured aneurysm (24% of patients). Earlier publications have demonstrated a peak in the incidence of rebleedings within 24 hours and in the end of first week after the initial bleeding, and there is high mortality related to rebleedings [124, 112, 252]. A recent prospective study on predictors of outcome after aSAH found preoperative rebleeding to be an independent predictor for unfavorable outcome [74]. Even though rebleeding before treatment did not come up as an independent risk factor for unfavorable outcome in our results, it seemed to be associated to higher mortality. Early timing of treatment (<24h) has been an attempt to decrease this problem, but the problem still exists.

A more active approach and early timing of occlusive treatment might be one part of the explanation why no patient died since 2000 while waiting for treatment, whereas before that, seven patients died. However, early timing of treatment (<24h) has not been shown indisputably to be superior to treatment within 72 hours [220]. The early rebleeding rate seems to be higher the more severe the initial bleeding is [112, 252], meaning that at times early rebleedings might be part of severe and difficult course of the disease, where even early timing of treatment cannot help these patients.

Occlusion Grade

The embolized PComA aneurysm patients required re-treatment in 27% of cases during the first year, whereas 4% of microsurgically treated patients needed re-interventions. Although the number of patients treated by endovascular means was limited, our results are in line with earlier publications reporting high recurrence rates (or new filling of the aneurysm neck) after coiling of PComA aneurysm [21, 221, 18]. There are also indications that flow diversion might be ineffective treatment for patients with fetal PComA [265]. About one third of PComA aneurysm patients have dominant or fetal PComA on the side of the aneurysm (Publication I). It seems that the need for additional treatment can expose patients to treatment-related morbidity later in life. This challenge of recurrence may lead to similar conclusions with an earlier publication stating that there is still need for microsurgical skills in treatment of PComA aneurysms, especially in some complex cases, including recurrence after coiling [232].

On-Going Changes in Treatment Methods and Limitations

As the study period on treatment of ruptured PComA aneurysms spans over three decades, it causes difficulties in interpreting the results. The clinical condition of hospitalized aSAH patients has changed, and the activity of treatment has become more aggressive. The acceptable standards and requirements for occlusive aneurysm treatment have evolved. The carotid ligations and trappings of the PComA aneurysm of the 80´s are no longer the first line treatment. There is also strong bias towards the microsurgical treatment method during the study period. This means that making comparisons between different treatment methods is not reasonable.

The retrospective setting should be taken into account when interpreting the results. After all, the study gives an all-inclusive view of all the treated patients with ruptured PComA aneurysms in a high-volume neurosurgical center, as only few patients were excluded. This study was able to reveal challenges related to the treatment of ruptured PComA aneurysms that have not been identified earlier by much smaller patient series.

Long-Term Excess Mortality after aSAH

Long-Term Excess Mortality (Publication III)

The long-term follow-up study on 3078 aSAH survivors showed that there is evident excess mortality among aSAH patients when compared to the general Finnish population. The excess mortality was 17% at 20 years and 32% at 30 years, and it was also present among the young and the patients who had made good recovery at 1 year after aSAH. This is in line with another follow-up study of 1746 aSAH survivors from Eastern Finland, which showed excess mortality of 12% at 15 years (cumulative RSR, 0.88; 95% CI, 0.85–0.91) [110].

There were only few previous studies on long-term survival of aSAH patients (follow-up more than 5 years), and some of the results were contradictory, especially concerning the survival of young patients and patients with initial good recovery. Most of these long-term follow-up studies showed, however, that patients with a history of aSAH seem to die earlier than their peers, even though the respective statistical methods used were different [200, 226, 268, 110, 141, 195, 187].

Risk Factors for Excess Mortality (Publication III)

The risk factors for long-term excess mortality after the statistical analysis were: (I) multiple aneurysms, (II) age (especially >60 years), (III) poor preoperative clinical condition, (IV) conservative treatment, and (V) unfavorable clinical outcome at one year. A totally new finding was the multiplicity of aneurysms being related to higher excess mortality in the long run, which seemed to be releted to the increased risk of lethal rebleeding during the long-term follow-up but even more to the general burden of other vascular disease. Other risk factors had been detected by some earlier studies, and were verified by this one [226, 268, 110, 141]. Earlier findings demonstrating that male gender or aneurysm location at the basilar tip would be risk factors for excess mortality 110 were not supported in our study.

As patients with multiple aneurysms had a three-fold risk of lethal rebleeding when compared to patients with a single aneurysm, an active approach towards prophylactic treatment of other aneurysms, in addition to the ruptured one, may be encouraged. Whether or not this will decrease the long-term excess mortality should be evaluated in future studies. As treatment of unruptured aneurysms also carry some risks, and other locations and morphologies are riskier than others, the evaluation should be individual and the timing of additional operations should be planned carefully. Consultation of a neurovascular team is recommended prior to treatment decision.

Long-Term Excess Mortality after ICA-PComA Aneurysm Rupture

We evaluated the effect of the aneurysm location on long-term survival. PComA aneurysms formed the majority, 88% of the ICA aneurysms (n=520 PComA aneurysms of all [593] ICA aneurysms in 1980–2007). Figure 38 presented the cumulative relative survival ratios of the patients, grouped according to their aneurysm location. The excess mortality was 20% at 20 years for patients with an ICA-PComA aneurysm (cRSR 0.80, 95% CI 0.74–0.86, Huhtakangas et al, unpublished results), meaning there is excess mortality also after PComA aneurysm rupture in the long run. There were no significant differences between groups with different aneurysm locations. The differences in the end of the curves are due to wide confidence intervals as the number of follow-up patients in each group decreases. No previous publication reports the long-term mortality specifically for PComA patients.

Causes of Excess Mortality

The leading causes of death in long-term follow-up after aSAH were cardiovascular disease (26%) and cancer (22%). These were common causes of death among the general Finnish population as well (30% and 23%, respectively). Cardiovascular causes of death were overrepresented especially among the younger age groups (<65-year-olds). An earlier study on 1765 aSAH patients also stated an increased risk of vascular disease and death pronounced in younger patients [195].

In addition to mortality caused by aSAH, which was highlighted during the first ten-year-period accounting for about one fifth of deaths, other cerebrovascular causes of death were prominent as well: they formed 16% of all causes of death in ≥65-year-olds and 12% of all causes of death in <65-year-olds. These proportions were higher than among the general population (10% for ≥65 years, 4% <65 years). A similar finding was reported by a study on 233 aSAH survivors, which showed long-term excess mortality caused by cerebrovascular events (SAH and others) in comparison to the general population (28% versus 8% of all deaths) [141]. A Dutch study has shown an elevated incidence of both cerebrovascular and cardiovascular events in patients after aSAH [268].

It would be important to understand why the patients surviving the aSAH are prone to develop other cerebrovascular and cardiovascular conditions in order to be able to attack the problem. A previous Finnish study on long-term follow-up of 1537 aSAH patients has proposed that the aSAH might be a manifestation of systemic vascular disease [226]. It is also possible that the initial strong stress reaction after aSAH, sympathetic nervous activation and systemic inflammatory response causes irreversible effects on the vessel walls and the whole vascular system. The third and quite probable cause may be the shared risk factor profile lying on the background of these diseases.

Active Treatment of Cardiovascular Risk Factors

Overall, considering our results and similar findings of previous studies, it seems that there might be increased risk of cardiovascular disease among younger patients and increased risk of cerebrovascular events irrespective of age. As smoking and elevated blood pressure are relevant risk factors for all of these conditions, efforts should be made to treat these shared risk factors. Patients surviving aSAH would probably benefit of systematic blood pressure monitoring and specified target levels in treatment, if necessary. The importance of ceasing smoking should be emphasized and discussed regularly with the patient if needed. The patients should be encouraged to take responsibility of their own health, and positive feedback should be given when patients have been able to change their habits for better. The patients should be guided to the general practitioner for regular check-ups and support after surviving aSAH.

It would be interesting to see if aSAH survivors would benefit from cholesterol medication or antithrombotic medication. These are widely used in secondary prevention after vascular ischemic events and in cardiac or systemic vascular disease, which share similar risk factors [229], [216], [48]. One challenge is that the effects on long-term survival are seen only after several years of follow-up. Further research on the issue would be necessary before making conclusions.

Need for Follow-Up

For decades, during microsurgical era in treatment of ruptured intracranial aneurysms, the need for follow-up after aSAH has been seen as minimal. The risk of rebleeding after treatment is low, and according to our results from Publication III, the risk of recurrence is highest during the first 5-year period after aSAH. In Helsinki, the aSAH patients had routinely a 3-month check-up and only patients with obvious neurological deficits or unable to work were guided for multi-disciplinary rehabilitation assessment. Many patients who were monitored for longer periods had additional aneurysms requiring treatment. However, many patients with good recovery after aSAH still suffer from neuropsychological symptoms and some of these challenges appear only months later, when they try to return to their previous activities [94], [13], [208], [88], [181], [214]. At times, the fatigue aSAH survivors may experience later on in life is not recognized as symptoms relating to the sequelae of aSAH, if the neuropsychological assessment has not been done after aSAH (Publication II, unpublished results). Probably most aSAH patients, especially those still aiming at participating in the working life, would benefit from neuropsychological evaluation during the rehabilitation period.

As endovascular treatment has increased in numbers, also the number of patients requiring imaging check-ups has increased to ensure the occlusion rate of the treated aneurysm. Another factor causing need for follow-up is the finding in Publication III that the risk of rebleeding from another aneurysm remained elevated decades after aSAH, and it was higher among patients with multiple aneurysms as well as among young patients. Because of this finding, our research group recommended an active approach in implementing preventive treatment of additional unruptured aneurysms, especially among the younger patients after aSAH. They may also benefit from a routine, late angiographic check-up (CTA or MRA), for example at ten years after the aSAH.

The long-term excess mortality and the risk of cerebrovascular and cardiovascular events emphasize the need for follow-up in general medical practice, like e.g. patients with diabetes or high blood pressure. Due to known risks related to these conditions, all these patient groups require regular guidance and support. Even though the group of aSAH survivors is smaller compared to groups of other conditions most common in public health, the loss of productive life-years caused by aSAH is significant 64, 121. Considering the mean age of patients at the time of aSAH (<60 years), the prevention of additional problems should be emphasized even more than nowadays.

Future Aspects

Changes in Occlusive Treatment Modalities

The endovascular treatment has become more common and nowadays about 50–60% of intracranial aneurysms are treated by endovascular means in Helsinki University Hospital, and the numbers are even higher in many neurosurgical centers

in the Western Europe and in the United States [165, 63]. Since the activity of endovascular treatment is increasing and developing at a quick pace, the treatment results should be reported regularly to stay up to date. Probably the endovascular development will continue and novel devices like self-expanding and shape-modifiable intraluminal devices will see the daylight. There are still challenges concerning the recurrence of treated PComA aneurysms, and these modifiable devices may give a better chance to occlude the aneurysm and yet to preserve the PComA. In the future, there will probably be medical therapies as well, which can be used to attack the unruptured aneurysms, to strengthen the wall and to prohibit the rupture.

Microsurgery will probably still be needed in the future in treatment of some morphologically complicated intracranial aneurysms, in aneurysms with large hematomas, in recurrent cases and in treatment of few specific aneurysm locations. Some centers already have used neurophysiological monitoring as a routine part of the microsurgical treatment [271]. As the occlusive treatment-related ischemia still causes impaired outcomes, there will probably be advances in usability and sensitivity of the intraoperative monitoring techniques. This might improve the ability to prevent occlusive treatment- related brain infarctions.

For ruptured aneurysms, fast and effective initial medical response and transfer of the aSAH patient to a neurosurgical unit will continue to be a challenge. Not only do the poor-grade patients need early operation for expansive intracerebral or subdural hematomas or hydrocephalus, but all aSAH patients need specialist care to minimize early brain injury and to reduce early rebleedings. There will also be a need for a simplified protocol for initial medical care and transfer of a poor grade neurosurgical patient. In Finland, distances to the closest neurosurgical unit can be long, and there should be novel innovations developed for minimizing delays in patient transfer. As the use of virtual reality develops, the neurosurgeon on call may be brought virtually to the operating room of a distant hospital, and the most urgent on-call operations may be performed in co-operation with the neurosurgeon and the local surgeon with a live feed and live interaction.

Virtual Hospitals and Improved Follow-Up of Patients

The development of national virtual hospitals is already in progress and it gives a chance of developing more individualized treatment plans and makes it possible for the patients to participate in their own treatment and health more than ever before. In virtual hospitals, patients will be able to have their own follow-up sites and individualized target levels, and they can keep track and get feed-back on their progress. Nowadays, personal trainers are a growing business in physical training and sports. In the future, a personal health coach or a personal medical professional might be even more common. On weekly appointments, they could help with health issues, with nutrition and exercise, with medications, with an abstinence plan or with mental health issues according to every patient´s individual needs. The health coach might even be provided by the public health system in order to improve the well-being and working ability of the citizens.

Nation-Wide and International Data Bases

The collection of digital patient data has already started, and in the near future, it is realistic that this data will be transferred to digital patient registers. Digital registers will be able to synchronize and communicate with the medical files of the patients, and they can be used to electronically collect questionnaires and follow-up data from the patients. This system enables nation-wide and even international registers, and systematic prospective collection of data for research purposes. As these registers will contain a large amount of information, the statistical power of the data analyses will improve and opens the door to using machine-learning algorithms. On the other hand, this requires professionals, data scientists, to handle all the information and to utilize these large registries for research purposes. The value of data analysis will rise to a new level and give valuable input to research.

Conclusions

I PComA aneurysms rupture also at small sizes (38% <7mm), and there are location-related morphological parameters that are independently associated with rupture: irregularity of the aneurysm dome, wider aneurysm neck and aspect ratio >1.5.

II Even though most treated aSAH patients recover relatively well after PComA aneurysm rupture, there are occlusive treatment-related complications related to all available treatment methods causing impaired outcome also among young and initially good grade patient. The rate of artery occlusions in postoperative angiography and occlusive treatment-related brain infarctions were higher than expected.

III PComA aneurysms may have been seen as fairly uncomplicated lesions, but they do not seem to be that easy or benign, at least when ruptured. Occlusive treatment of a ruptured PComA aneurysm seems to be a high-risk procedure even in a high-volume neurosurgical center.

IV There is constant excess mortality after aSAH in a long-term follow-up, and it is present also among young patients and patients with initially good recovery after aSAH.

VI Cardiovascular events at younger ages and cerebrovascular causes irrespective of age were overrepresented as causes of death, which encourages the treatment of vascular risk factors.

VII Lethal rebleedings, from previously treated or from another aneurysm during the long-term follow-up, in addition to higher excess mortality, were more pronounced in patients with multiple aneurysms compared to patients with a single aneurysm.

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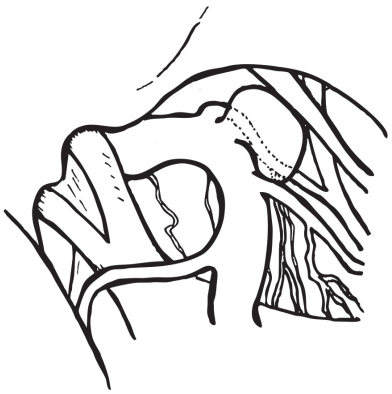
ANEURYSMAL subarachnoid hemorrhage (aSAH) is a serious form of stroke, caused by a ruptured intracranial aneurysm, that often strikes at the working age. The origin of the posterior communicating artery (PComA) is one of the most common locations for ruptured aneurysms causing aSAH. There are specific features related to the risk of rupture, severity of bleeding and occlusive treatment of PComA aneurysms, identified in few previous studies.

It has been believed that after successful rehabilitation aSAH patients should have a similar life-expectancy to that of the general population. However, lately there have been indications of excess mortality in the long run, at least among some aSAH patient groups.

The aims of this work are 1) to identify the morphological features related to PComA aneurysms and their rupture, 2) to study the treatment and outcome after PComA aneurysm rupture and aSAH, 3) to discover if there is long-term excess mortality after aSAH compared to the general population.



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